In re Application of:
Rheins and Morhenn
Application No.: 09/375,609
Filed: August, 17, 1999
Exhibit A - Page 1

PATENT
Attorney Docket No.: DERM1100-1

EXHIBIT A:

COMMENTS OF NIH REVIEWERS OF NIH GRANT APPLICATION NUMBER 1 R43 AR049110-01

Alan Moshell M.D.
301-594-5017
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SUMMARY STATEMENT
(Privileged Communication)

Release Date: 04/15/2002

Application Number: 1 R43 AR049110-01

BENSON, NICHOLAS R, PHD
DERM TECH INTERNATIONAL
15222-B AVENUE OF SCIENCE
SAN DIEGO, CA 92128

Review Group: ZRG1 GMA-1 (10)
Center for Scientific Review Special Emphasis Panel

Meeting Date: 03/18/2002
Council: MAY 2002
Requested Start: 07/01/2002

PCC: 4

Project Title: Non-Invasive Recovery of RNA from Human Epidermis

SRG Action: Priority Score: 205 Percentile:
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 1A-Both Children and Adults, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	121,700	188,818
TOTAL	121,700	188,818

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

NOTE TO APPLICANT FOLLOWS SUMMARY STATEMENT

NEW INVESTIGATOR

BENSON R43AR049110-01

RESUME AND SUMMARY OF DISCUSSION: This proposal is to use a non-invasive tape stripping to recover mRNA from human epidermis for study. There is novelty in the concept and some research benefits may accrue. Concerns that diminished enthusiasm relate to problems of sensitivity and specificity. In diseased skin, tape stripping will not be cell specific owing to lymphocyte and neutrophil exocytosis. And in cleansed skin to remove "foreign" mRNA, "cleansing" could remove native cells. Nevertheless, the reviewers were impressed by the innovation and the potential of the approach.

DESCRIPTION (provided by applicant): The goal of the proposed research is to optimize a patent-pending methodology for the non-invasive recovery of RNA from the upper layers of human epidermis. Current methods for sampling the nucleic acid contents of the skin rely exclusively on biopsy of the dermal and epidermal layers. Because many patients prefer not to subject themselves to surgical procedures, potentially valuable clinical information is not obtained. Therefore, there exists a rather large region between "afflicted" skin and "must-biopsy" skin for which there exists no sensible molecular data, collection technology. Furthermore, the use of biopsies for routine clinical testing of non-prescription skin treatments is not viewed as a practical means of generating clinical data. If a sampling method were available, which could non-invasively, accurately, and reproducibly harvest nucleic acids of the epidermis, this method would gain widespread clinical acceptance and fill a discernable medical void. This proposal aims to identify optimal tape stripping products; optimize the extraction of nucleic acids from the tape; and demonstrate the utility of the methodology in a clinical study. We expect the success of this technology to enhance and accelerate the diagnosis of dermatological diseases and molecular profiling of the skin.

CRITIQUE 1: Resume: This is an excellent proposal to test an innovative idea that could fill an important commercial and scientific need. The assumption on which it is based (mRNA in outer stratum corneum) and variability of data are causes for reduced enthusiasm.

SIGNIFICANCE (& COMMERCIAL POTENTIAL): A non-invasive, quick, sensitive, quantitative and reproducible method for performing gene expression profiling on epidermis would likely find wide application and commercial success. It could be used for diagnosis and to monitor response to insult or treatment. The proposal to analyze taped-stripped epidermis has obvious advantages over similar analysis performed on skin biopsy specimens.

APPROACH: This application builds on a single published work and preliminary data indicating that mRNA can be isolated and quantified from the stratum corneum. The approach is logical, direct, and convincing. The concerns relate to several unexpected and disconcerting results: 1. Existence of intact cellular mRNA in the outermost layer of St. corneum is surprising; 2. Recovery of more of this mRNA in one than two tape strips is anti-intuitive; 3. 100-fold difference between individuals suggests inherent assay variability or randomness in sampling. This could dilute its significance as a diagnostic or analytic tool.

INNOVATION: This proposal is highly innovative, in large part because most investigators would not have expected significant mRNA in outer layer of S.C. Its ultimate success will ultimately rest on the constancy and validity of that observation.

INVESTIGATORS: The principal investigator has limited experience in skin research, but is well equipped to lead the analytic effort. The consulting dermatologist is in private practice, and no CV was submitted for him.

ENVIRONMENT: The applicant company has a strong dermatologic advisory board. The laboratory is small; there is no way to assess surrounding scientific environment. There are no biohazards.

Budget: Majority of budget is for sensitive, sophisticated equipment - which is justifiable to perform sufficient controls to get a handle on the variability of their assays.

Human subjects: G1; M1; C1 (over 18)

Animals: N/A

CRITIQUE 2: RESUME: They propose to use tape stripping to recover RNA from the stratum corneum with the goal of following gene expression using the epidermal tape-stripping technique via quantitative PCR or DNA microarrays and making "molecular diagnoses" of skin diseases.

Novel and good potential, but the objective is somewhat naive. Their first goal should be to develop and show a reproducible method, that is, specific aims 1 and 2. Specific aim 3 is to look at IL-8 and TNF alpha versus control humans.

SIGNIFICANCE: The idea of this grant proposal is novel and very advanced. This work would be the beginning of real molecular diagnoses in dermatology. It has the potential of making the overall entire field and discipline of dermatology revolutionized towards a more objective science for making the diagnoses and modulating therapy according to gene expression.

APPROACH: They propose to use tape stripping to recover RNA from the stratum corneum with the goal of following gene expression using the epidermal tape-stripping technique via quantitative PCR or DNA microarrays and making "molecular diagnoses" of skin diseases. Much of this is based on a paper of Dr. Vera Morhenn. Their preliminary data raise the question of reproducibility of the results.

The first specific aim is to find the optimal tape product for tape stripping the skin for the purposes of isolating RNA and the number of times necessary to strip with the product to obtain the most RNA. The wish to optimize the RNA extraction conditions with the readout being quantitative RT-PCR indicated as a Ct value. Specific Aim 2 is also one that seeks to examine variability and the ability to detect changes in specific mRNAs versus housekeeping mRNAs. They will examine if there are changes in the mRNAs for IL-8 and TNFalpha versus housekeeping mRNAs in 10 human beings in which these mRNAs are measured at different but nearby skin sites. This will answer if there is site-to-site variability within a given person and also the variability between different subjects. Assuming aims #1 and #2 prove positive (i.e., ability to recover mRNA and have good Ct values with excellent reproducibility and minimal variability), in Specific Aim #3, they will do another human clinical trial and measure Ct values of the same cytokines under the influence of induced inflammation with topical SLS under occlusion versus vehicle and also compare the tape stripping with a punch biopsy.

The investigators have planned a logical set of experiments for optimization of the method and have correctly honed in on the issues of reproducibility, variability, and the ability to detect meaningful changes in Ct values in at least one skin perturbation (i.e., SLS- induced inflammation versus control vehicle).

There was some concern about the over-all view of the investigators about skin biology and their hope that mRNA detection on the very superficial samples obtained from tape stripping would reflect salient mRNAs and DNA products that reflect what is going one in lower layers of the epidermis and the dermis. The investigators should make finer correlations of what is obtained with tape stripping compared to that obtained from suction blister samples of whole epidermis and standardized biopsies.

This would give firmer credibility to the methods. Nevertheless, the importance and novelty of this approach was so strong that this minor criticism was noted and the suggestion encouraged, but not enough to damper seriously our enthusiasm.

INNOVATION: See Significance above.

INVESTIGATORS: There is an excellent advisory board (G. Krueger, D. Sauder, T. Franz, etc.). The principal investigator has a Ph.D. degree in molecular biology from UCLA and a modest record of publication. Nevertheless, the principal investigator and his investigative team are experienced and well trained and will be able to conduct the experiments outlined in the proposal or find the appropriate collaborators.

ENVIRONMENT: They have 750 square feet of laboratory space and 2000 square feet of clinical space and are currently constructing another 500 square foot addition to the laboratory space. This is an adequate environment to do the planned investigations.

Commercial Potential: Excellent commercial potential if improved, perfected, and proves reliably reproducible in the clinic situation. It would require some education of practicing dermatologists and a standardized procedure. Nevertheless, this could have wide applicability in the clinical setting for making more precise diagnoses and more precisely following objective parameters for therapy of skin diseases.

BIOHAZARDS: No concerns

HUMAN SUBJECTS: More detail should be provided about the human subjects that will be used. Based on the limited information available, however, it appears that their human subject use is:

G = 1A (both genders); M = 1A (both minority and nonminority); C = 1U (children not excluded. This reviewer does not believe that children need to be part of this initial study group; the investigators should justify the use of children as subjects.

GENDER MINORITIES CHILDREN: see above

ANIMAL WELFARE: Not applicable.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW ADMINISTRATOR TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE. The application proposes to study subjects between the age of 18 and 65. Children under the age of 18 will, therefore, not be included as study patients. This is appropriate.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

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Rheins and Morhenn
Application No.: 09/375,609
Filed: August, 17, 1999
Exhibit B - Page 1

PATENT
Attorney Docket No.: DERM1100-1

EXHIBIT B:

BUNGE, A. AND R. GUY (2003), "IMPROVEMENT OF METHODOLOGY FOR ASSESSING BIOEQUIVALENCE OF TOPICAL PRODUCTS"
http://www.fda.gov/ohrms/dockets/ac/03/slides/3996S2_07_Bunge.pdf

Dermatopharmacokinetics:

Improvement of Methodology for Assessing Bioequivalence of Topical Products

Annette L. Bunge

Chemical Engineering Department

Colorado School of Mines (CSM)

Golden, Colorado

Richard H. Guy

Université de Genève,

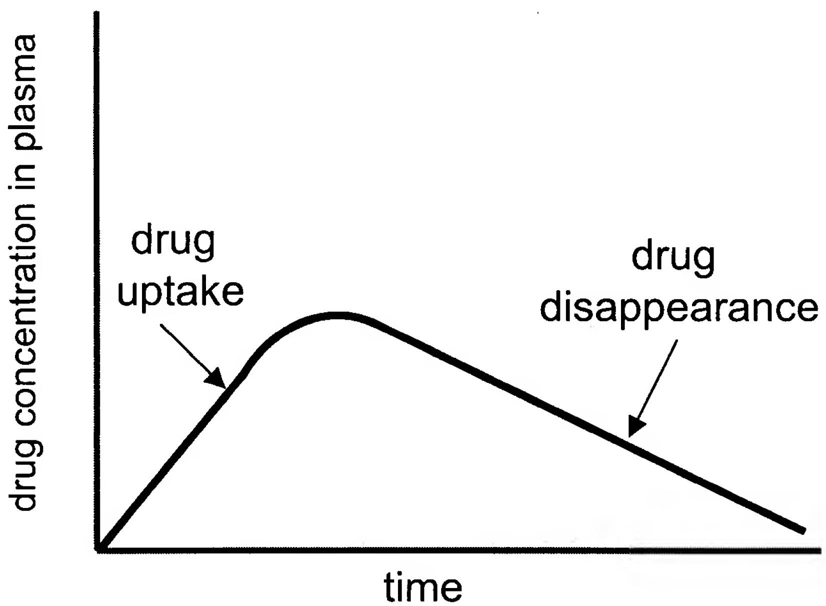
Suisse centre interuniversitaire de recherche et d'enseignement,

Universites de Geneve et Lyon, France

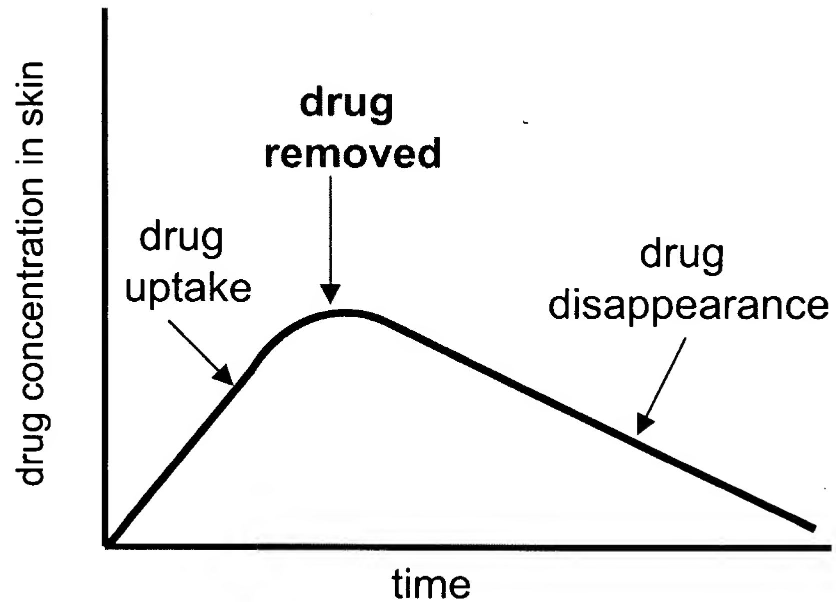
FDA:ACPS, October 22, 2003

DPK for topical drug assessment

Similar to pharmacokinetic methods for oral drug assessment



oral drug assessment



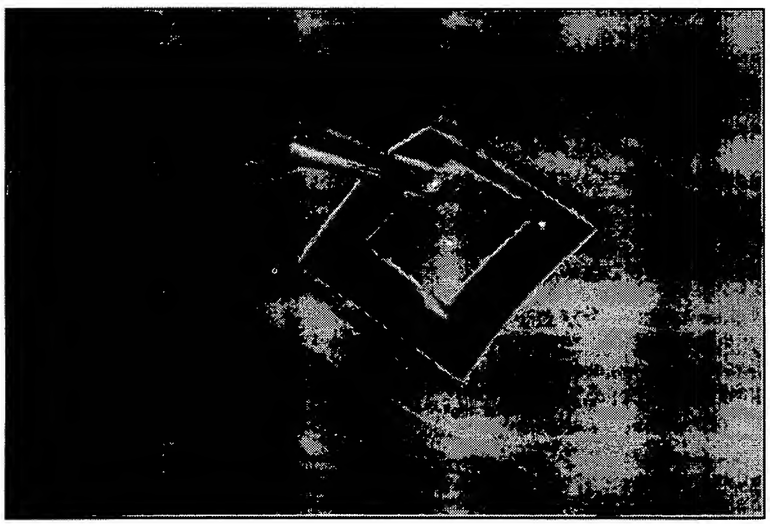
topical drug assessment

The motivation for a DPK method

- Clinical trials are...
  - Expensive, time-consuming, “relatively insensitive”
- Need to facilitate formulation development and regulatory approval while assuring safety/efficacy
  - BA/BE assessment of generic topical dermatological drugs
  - New topical formulations
- For topicals, there are few recognized ‘surrogate’ measures available to replace clinical studies
  - For certain compounds, a ‘pharmacodynamic response’ may be used to assess BE
  - e.g., the vasoconstriction (skin blanching) assay for corticosteroids

Sampling the Skin: *Tape stripping*

Determination of drug concentration in the stratum corneum (SC) by sequential removal of thin layers of SC at the same site with adhesive tape.



Sampling the Skin: *Tape stripping*

- Relatively non-invasive means of determining distribution of active within the SC
  - Removal of successive SC layers and assaying active concentrations therein

- Basis of the FDA "Dermatopharmacokinetic" (DPK) approach
  - Evaluation of topically applied levels in the *SC*, *in vivo*, as a function of time post-application and post-removal of the formulation

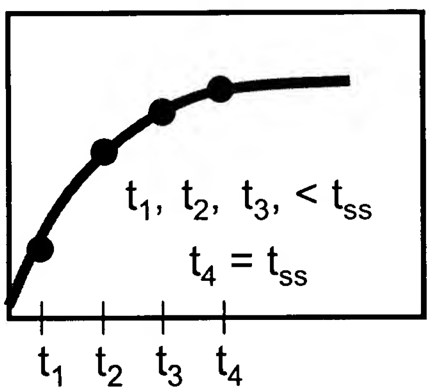
Assumptions for DPK: *Tape stripping*

- For normal, intact skin, the SC is (usually) the rate-determining barrier to percutaneous absorption.
- Concentration of active in *SC* is related to that which diffuses into underlying viable epidermis.
- Assessment of local efficacy using *SC* levels is useful and relevant.

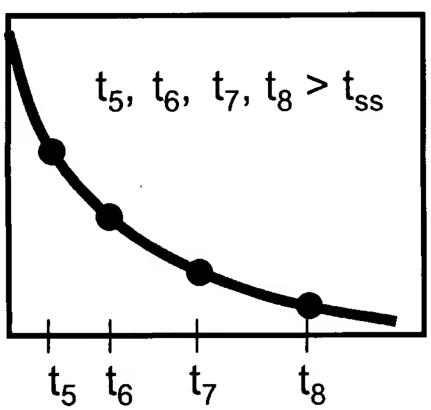
DPK bioequivalence study

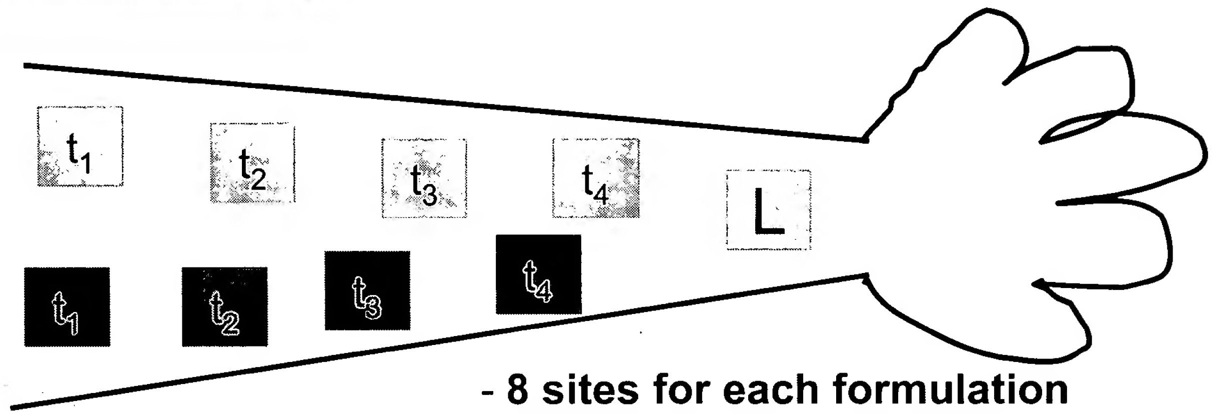
test versus reference

Uptake of active

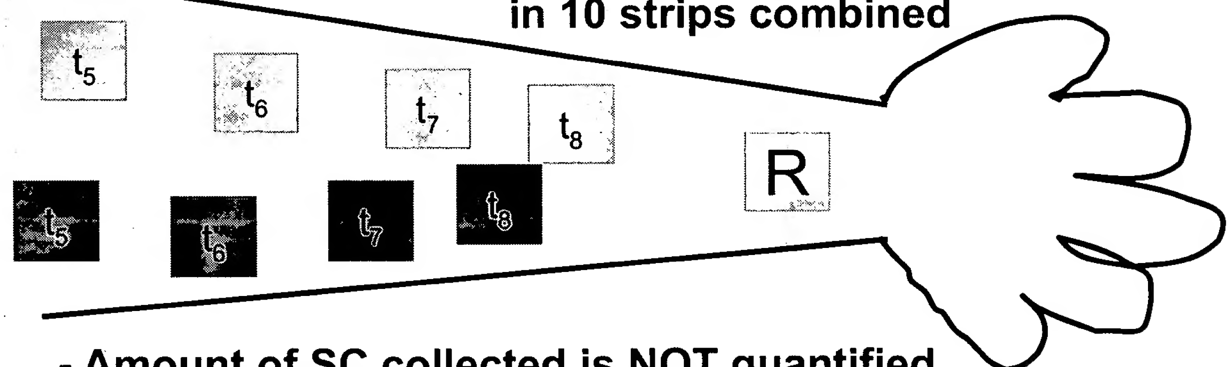


Elimination of active





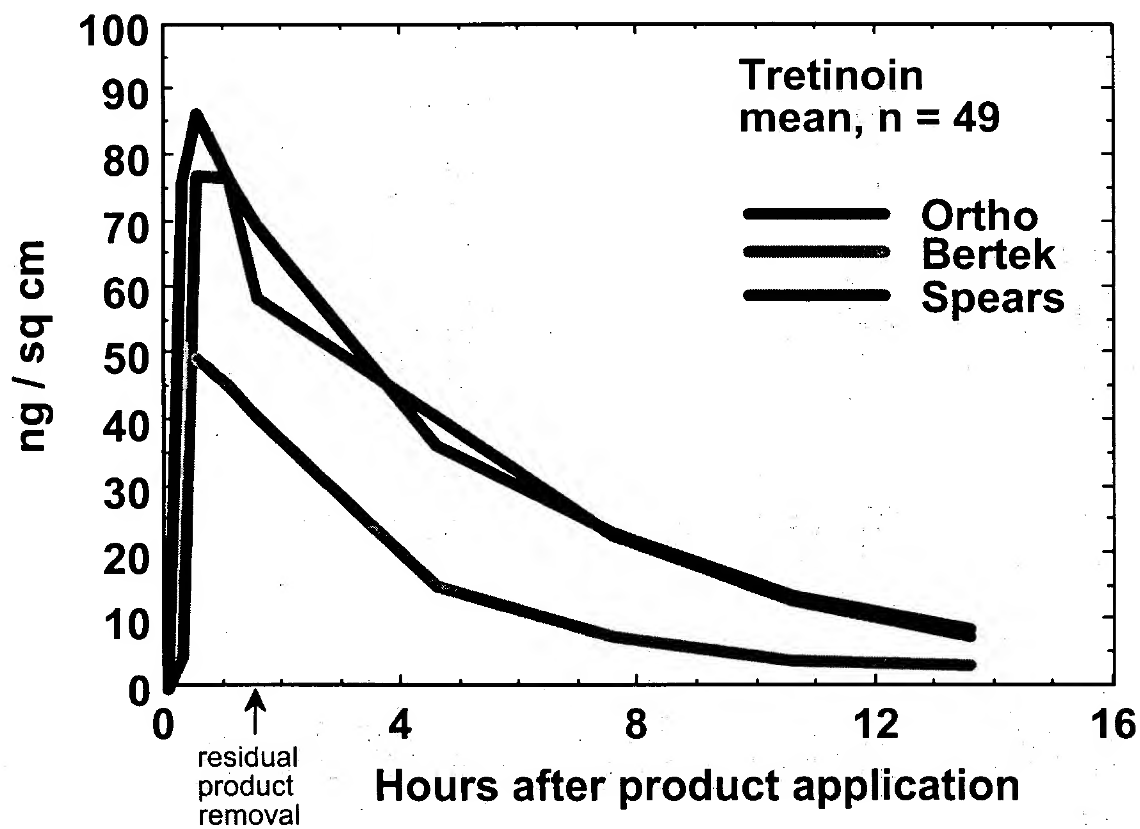
- 8 sites for each formulation
- 12 tape strips collected
- First 2 strips “discarded”
- Mass of drug/area determined in 10 strips combined



- Amount of SC collected is <u>NOT</u> quantified
- This is like measuring blood level without controlling volume

DPK bioequivalence study: *Example 1*

DPK bioequivalence assessment
Tretinoin gel, 0.025%



Drug Removed

0.25, 0.5, 1, 1.5 h

Tape Stripped

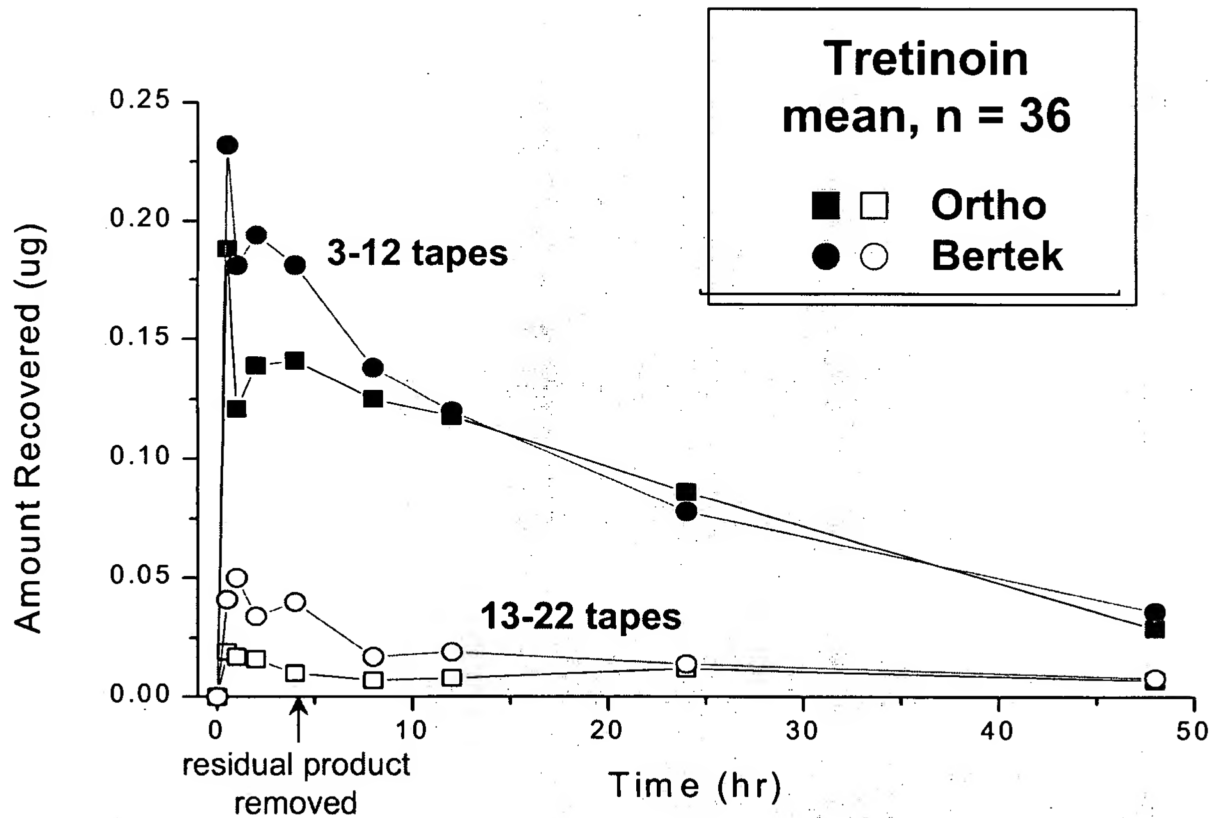
0.25, 0.5, 1, 1.5 h
3, 6, 9, 12 h

Ortho = Spears
Ortho ≠ Bertek
Ortho > Bertek

Pershing et al., 2003

DPK bioequivalence study: *Example 2*

DPK bioequivalence assessment
Tretinoin gel, 0.025%



Drug Removed

0.5, 1, 2, 4 h

Tape Stripped

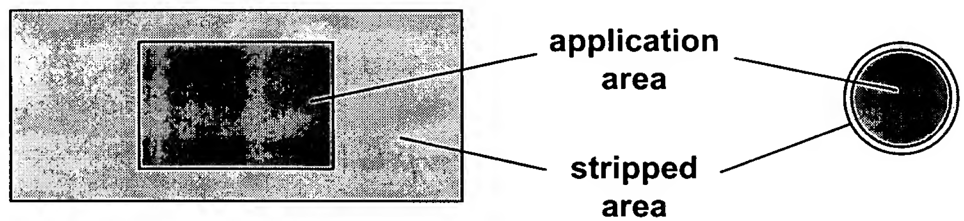
0.5, 1, 2, 4 h
8, 12, 24, 48 h

Ortho ≠ Bertek
Ortho < Bertek

Franz, FDA-ACPS, 11/29/2001

Why the lab-to-lab differences?

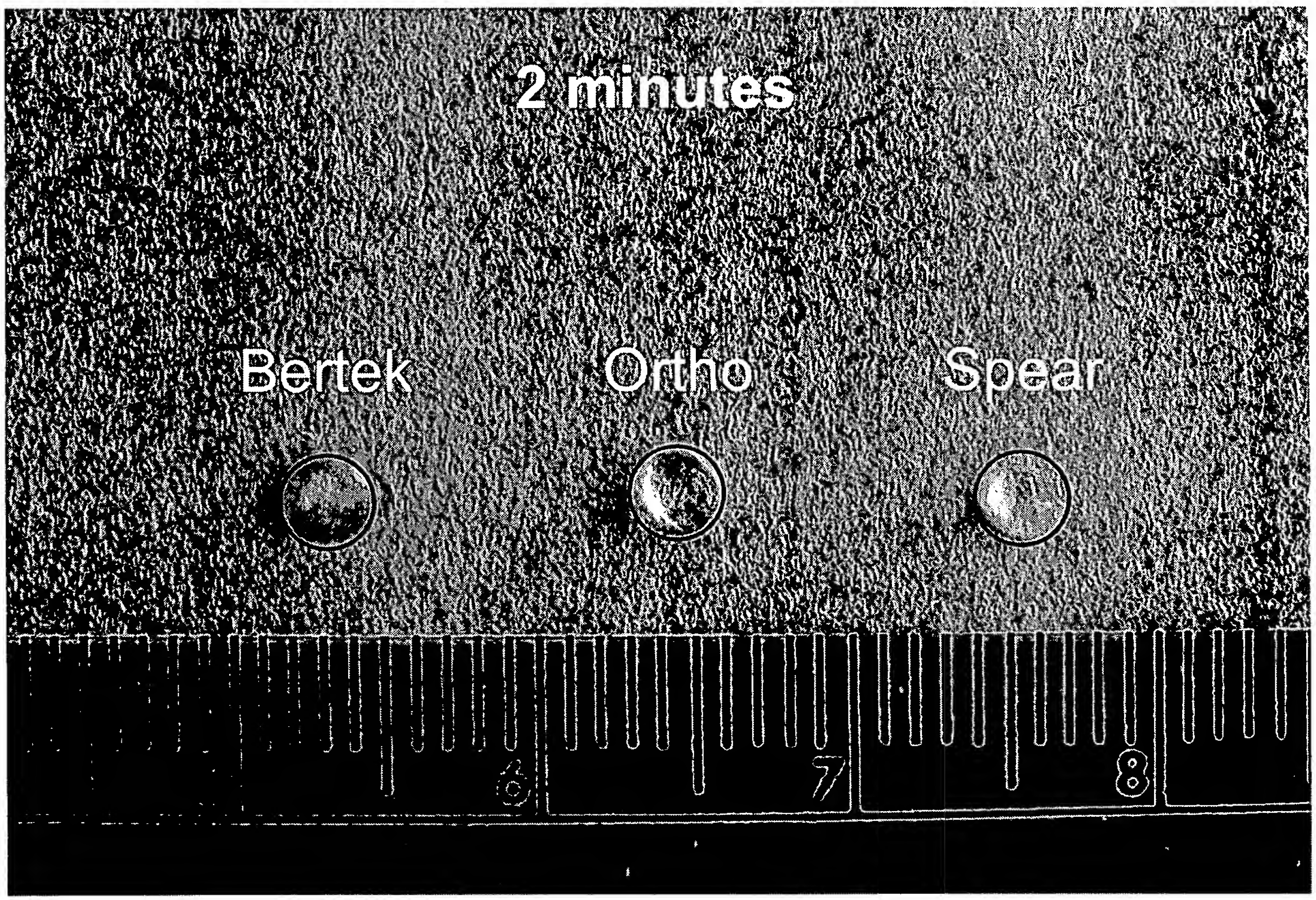
Control of application area



	Franz	Pershing *et al.*
Area of Application	4 cm^2 (uncontrolled)	1.13 cm^2 (controlled)
Amount Applied	20 μL	5 μL
Area Stripped	10 cm^2	1.33 cm^2
Tape Used	Transpore (3M)	D-Squame (Cuderm)

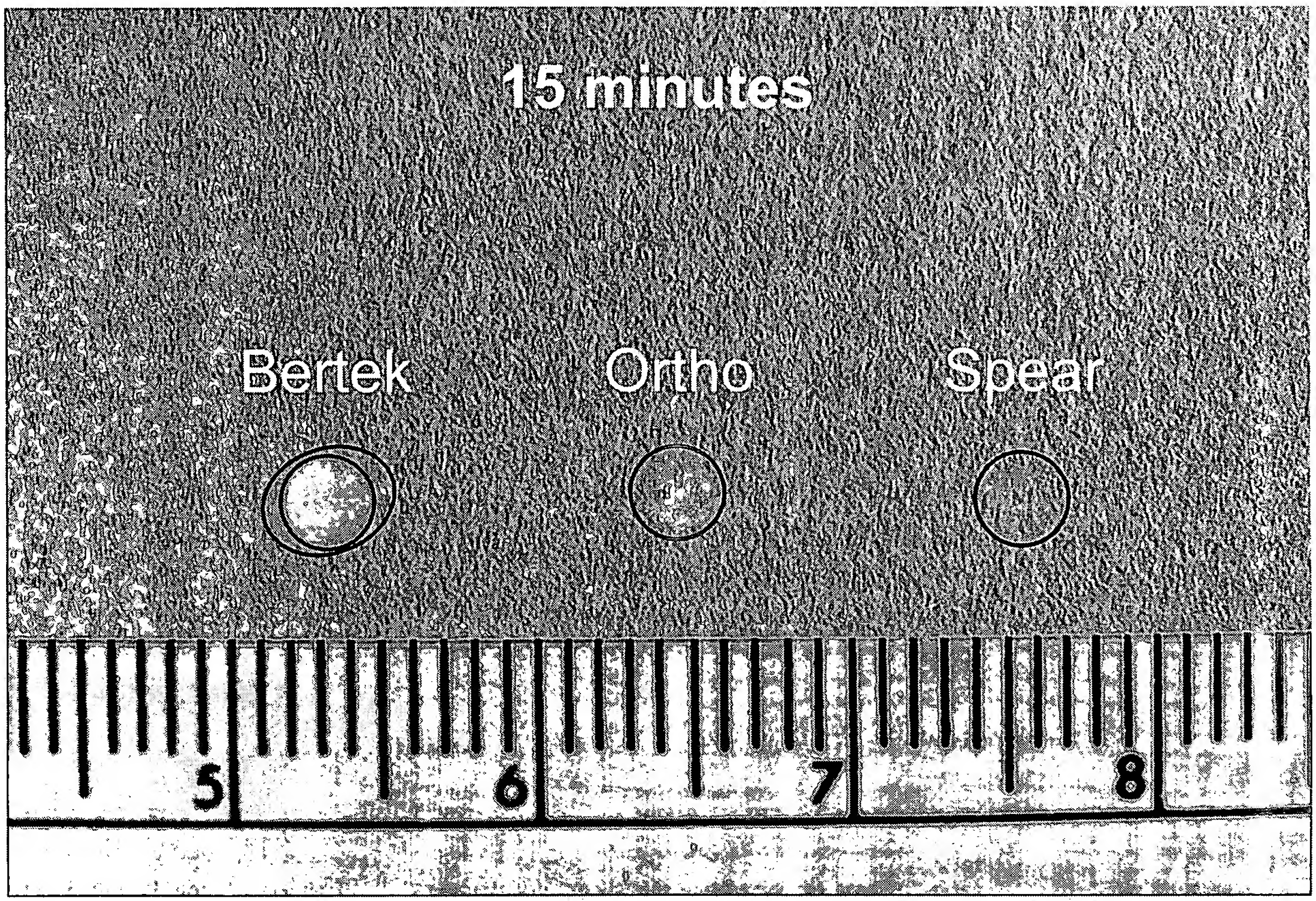
Why the lab-to-lab differences?

Control of application area



Why the lab-to-lab differences?

Control of application area



Concerns about the DPK method

- Reproducibility of the method between laboratories
- Effect of excipients on skin permeability or therapeutic effect
- Healthy versus diseased skin
- Adequacy of DPK method to assess BE of topical products for which the SC
  - Is not the target organ, or
  - Is not the sole limiting barrier (other pathways exist)

DPK: *Where are we now?*

- Draft guidance was withdrawn May 2002
- DPK is a new and “immature” method
- With further development and limited application, DPK has important potential
- Reducing variability in DPK data is essential
  - Reduce lab-to-lab variability
  - Need to reduce the number of subjects
    - 36 and 49 in the retin-A studies
    - 8 sites/drug & 2 drugs & 50 subjects = 800 experiments
- Sources of variability must be identified

DPK: *Identifying sources of variability*

- New 1-year contract with CSM and U Geneva to begin this process
- New DPK data will be collected
- Thorough examination of previous DPK measurements from our laboratories
- Combine experiments with mathematical modelling of dermal absorption mechanisms to identify the key issues

Sources of Variability: *SC Collection*

	Subject 1	**Subject 2**	**Subject 3**	**All Subjects**
*Mass of SC Collected (μg)	313.4	254.1	225.7	**264.4**
SD	85.5	45.4	60.6	**73.2**
CV%	**27.3%**	**17.9%**	**21.8%**	**27.7%**

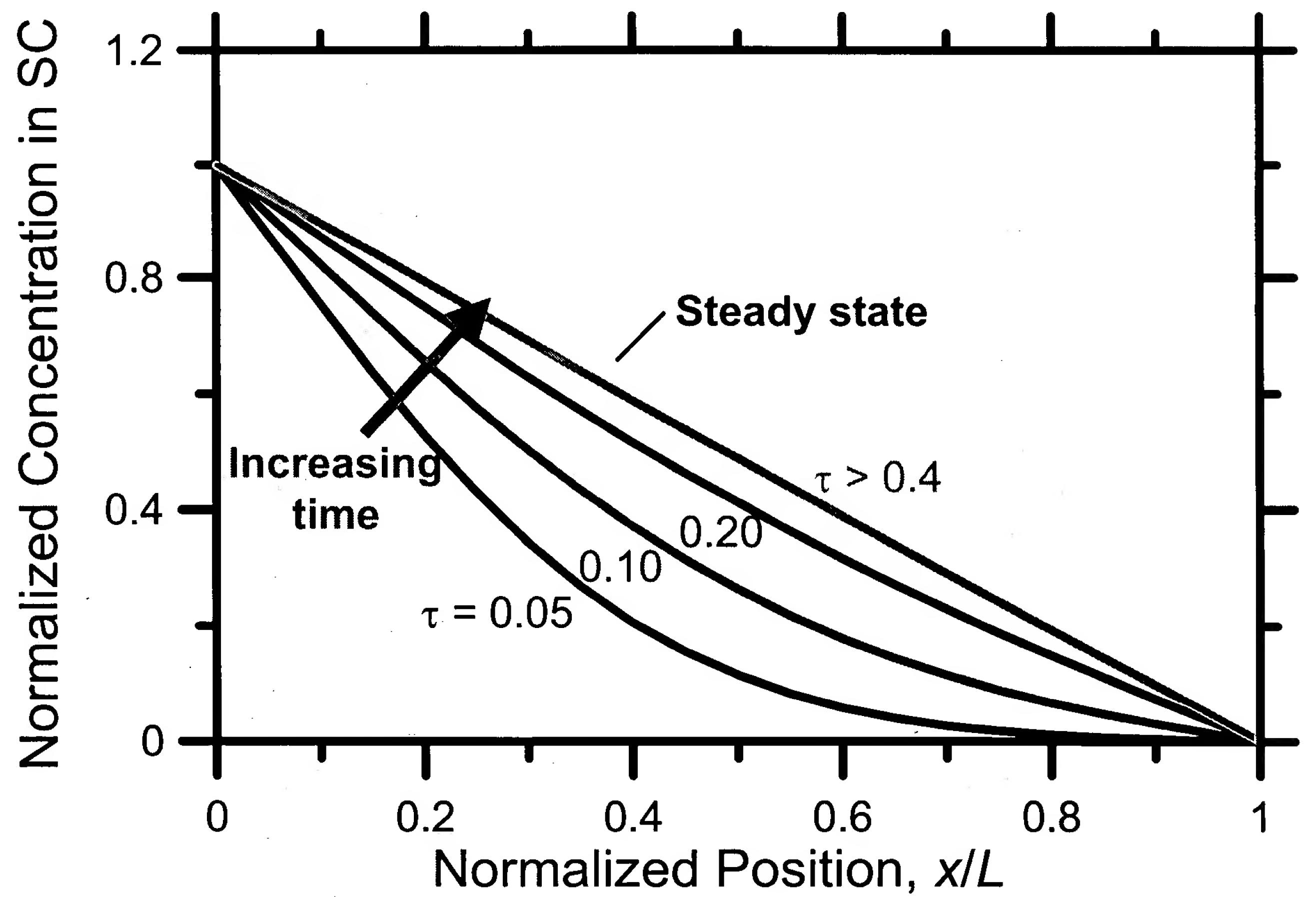
*Average of 8 sites, 4 sites on each arm. The same operator for all subjects.

Even for the same operator:

- **The amount of SC collected is highly variable**
- **Variability is the same <u>between</u> subjects and <u>within</u> subjects**
- **The amount of SC collected changes with depth (data not shown)**
- **How does variable SC collection affect the DPK result?**

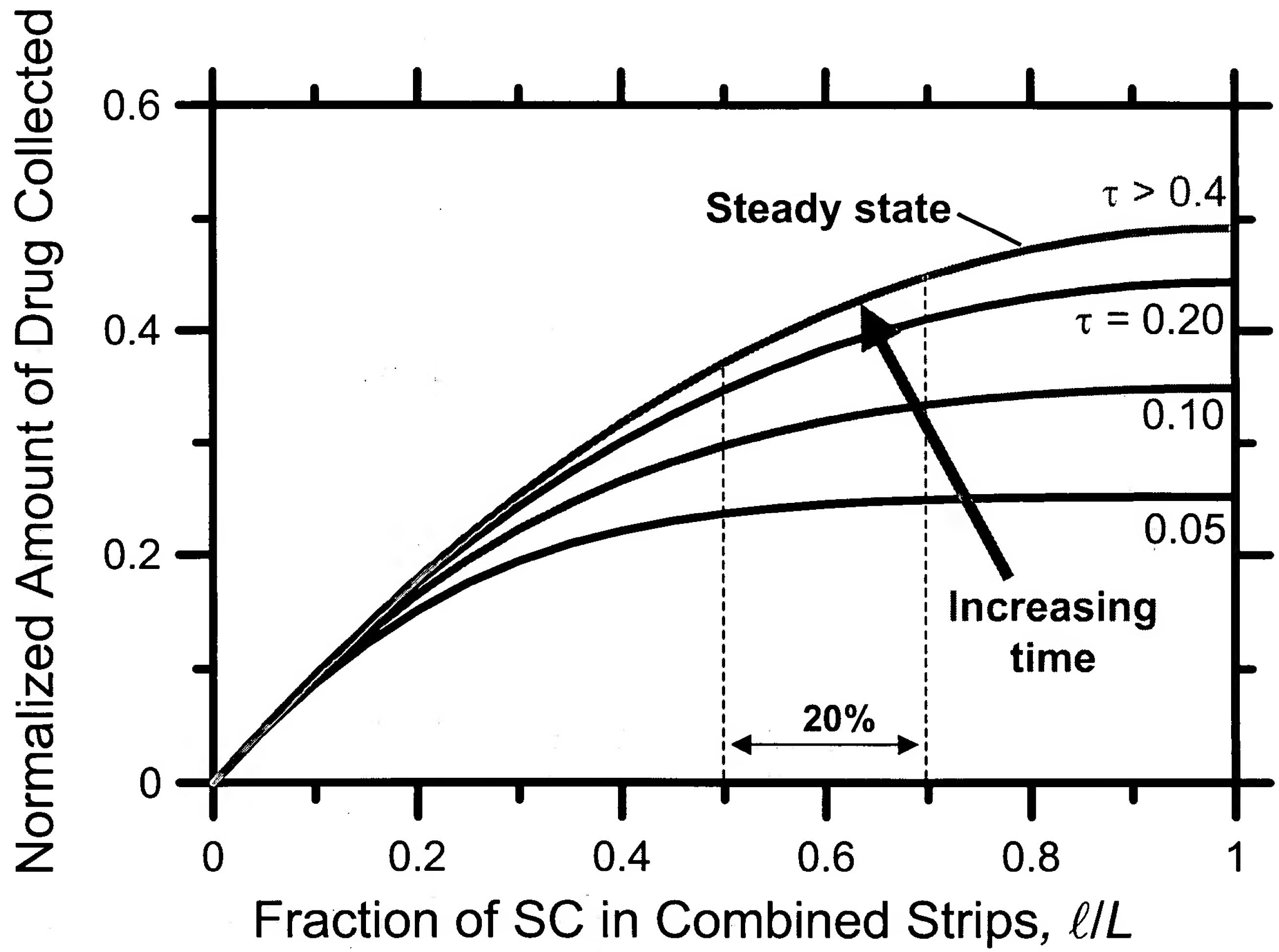
Pershing *et al.*, *Pharm Res*, 19:270-277 (2002)

Uptake

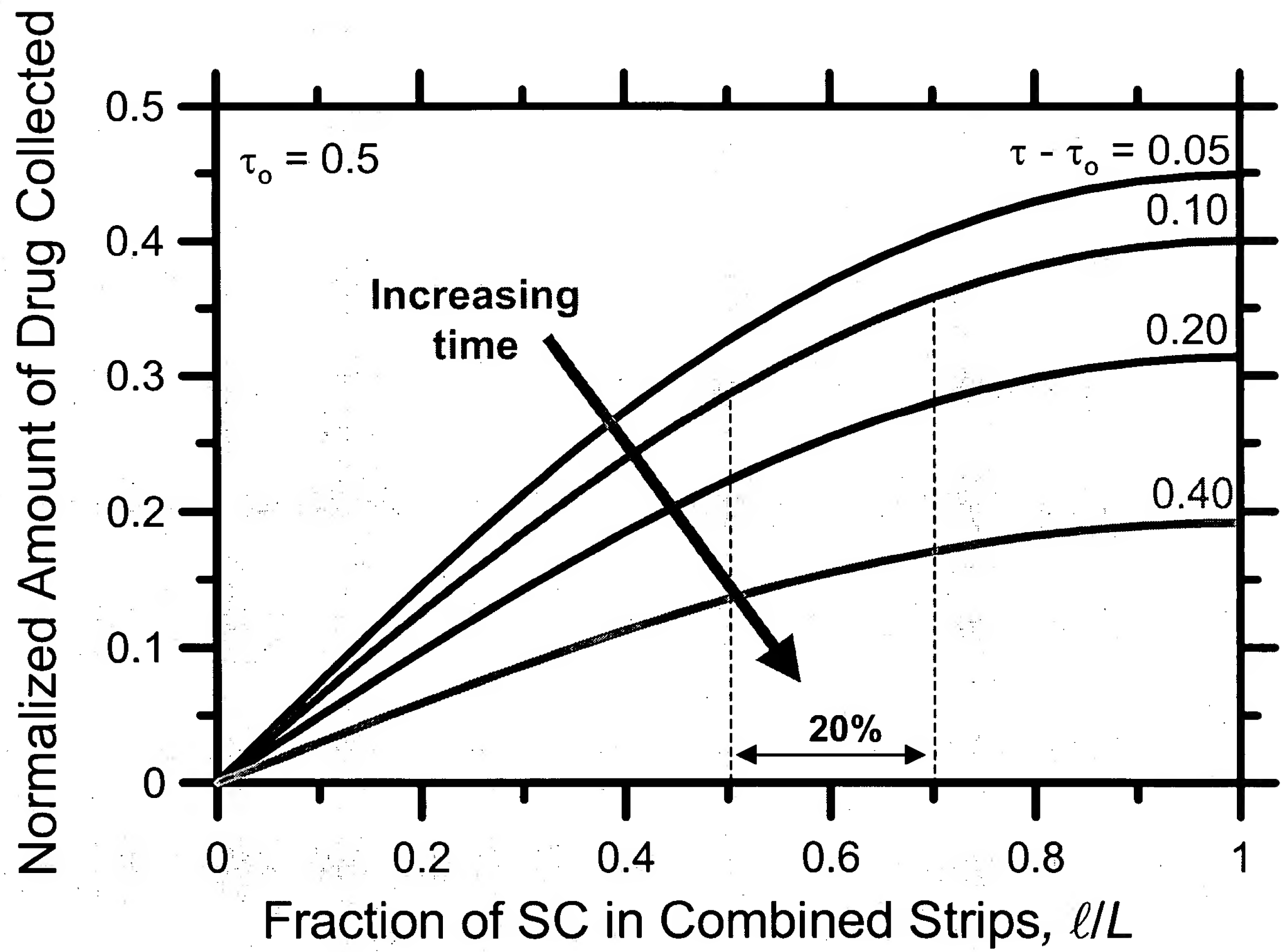


Normalized Concentration in SC
1.2
0.8
0.4
0
0
0.2
0.4
0.6
0.8
1
Normalized Position, x/L
Steady state
τ > 0.4
0.20
0.10
τ = 0.05
Increasing time

Uptake: *Effect of Variable SC Collection*

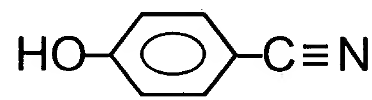


Clearance: *Effect of Variable SC Collection*



DPK Data: *Effect of Variable SC Collection*

Uptake and Clearance of 4-cyanophenol (CP)



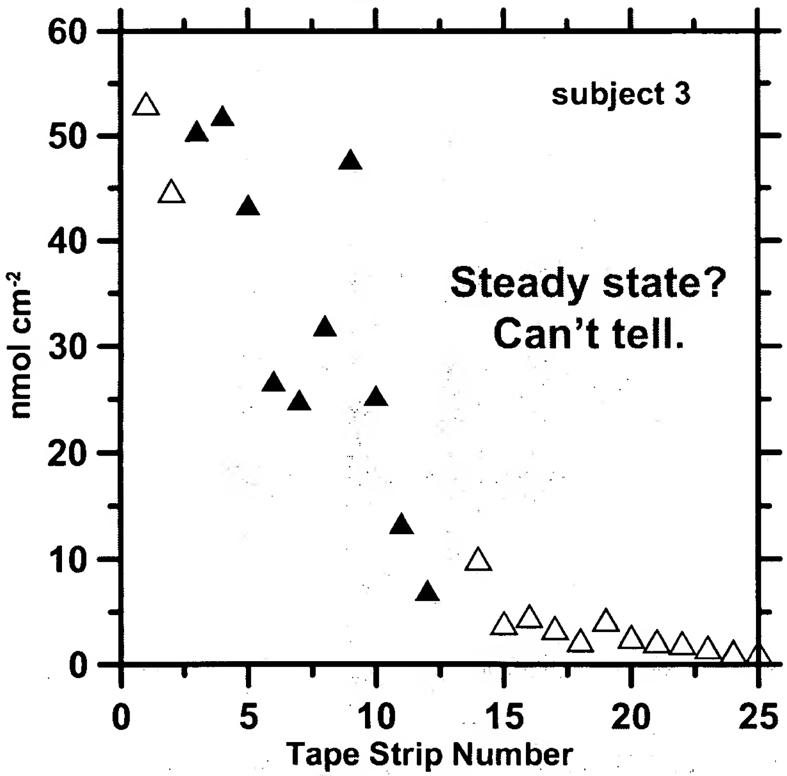
- Applied in a saturated solution of water
- Tape stripping
  - After 1 hour uptake (steady state?)
  - After 1 hour clearance
- For each tape strip, we determined
  - Mass of SC collected
  - CP concentration

Reddy et al.,Pharm Res, 2002o

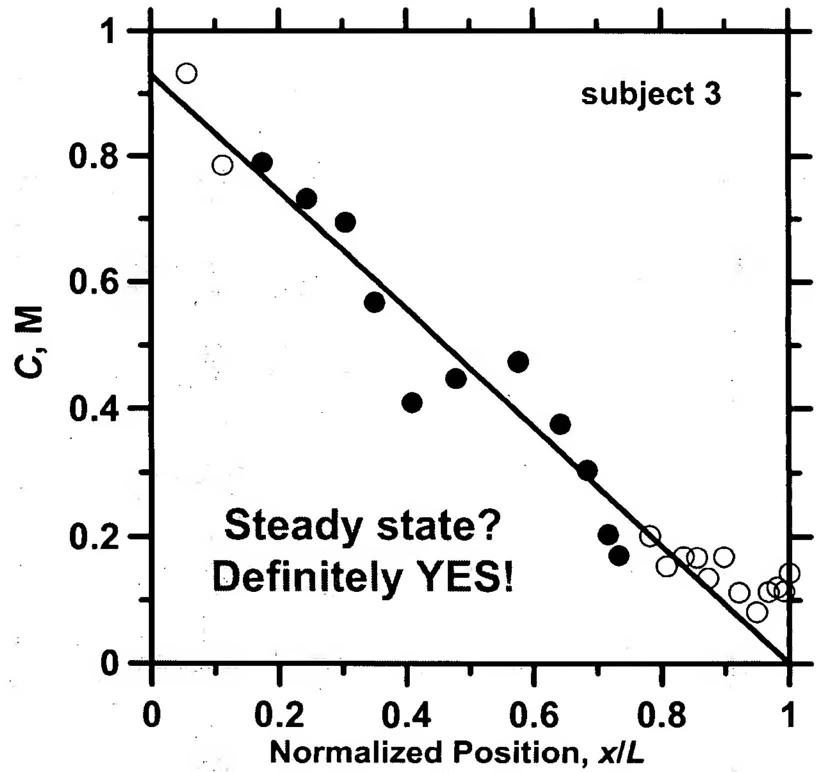
DPK Data: *Effect of Variable SC Collection*

Uptake

Amount of Drug =
320 nmol cm^{-2}



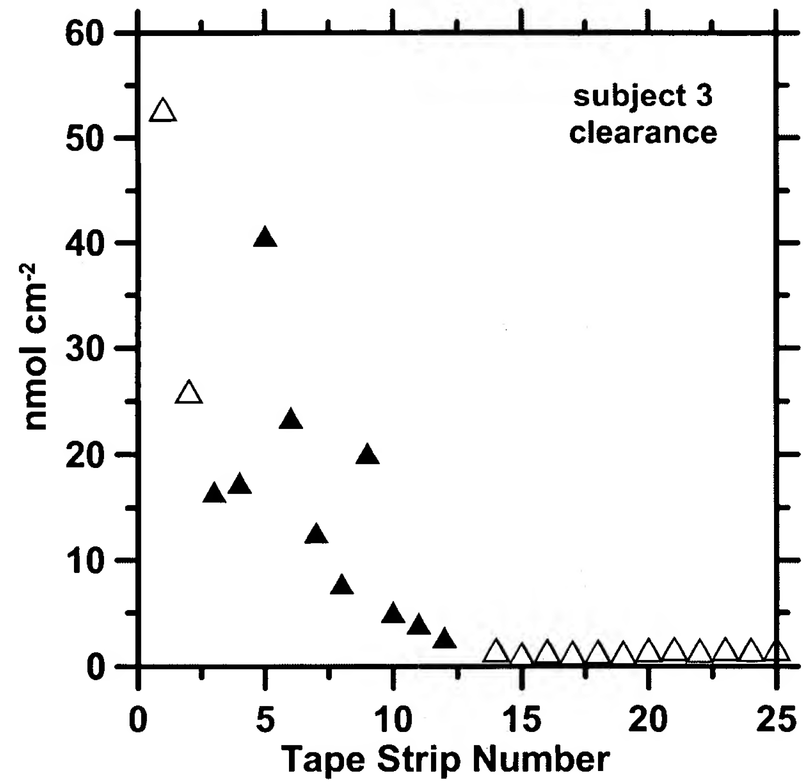
Average Drug C =
0.465 M



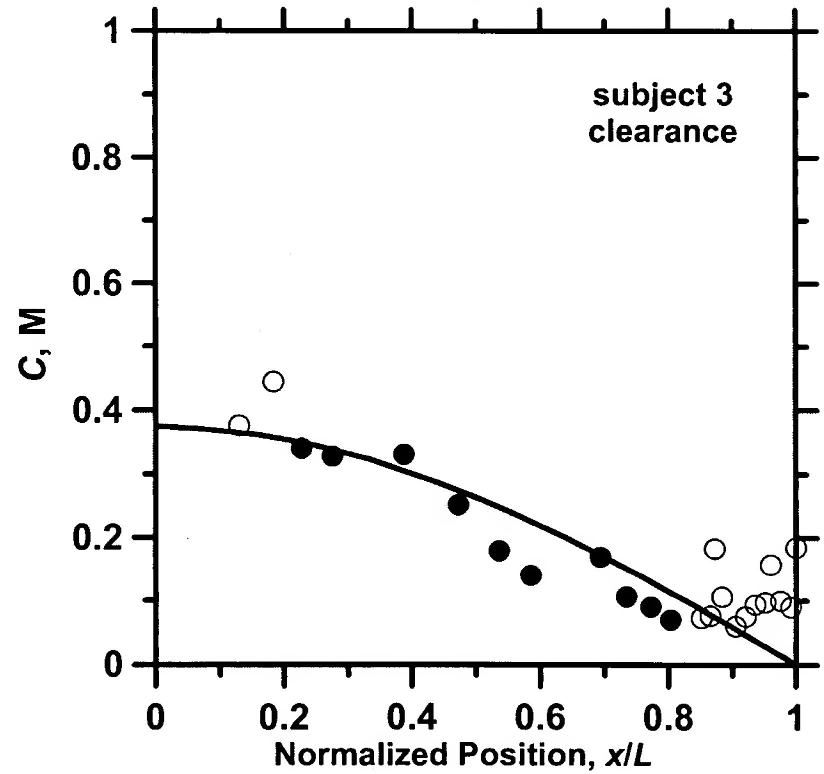
DPK Data: *Effect of Variable SC Collection*

Clearance

Amount of Drug =
147 nmol cm^{-2}



Average Drug C =
0.237 M



DPK Data: *Effect of Variable SC Collection*

	Uptake Phase		Clearance Phase	
	Average C (M)	**Amount/Area (nmol cm^{-2})**	**Average C (M)**	**Amount/Area (nmol cm^{-2})**
Subject 1	0.548	372	0.260	209
Subject 2	0.534	258	0.236	117
Subject 3	0.465	320	0.237	147
Mean	0.516	317	0.244	158
SD	0.045	57	0.0136	47
CV%	**8.6%**	**18.0%**	**5.6%**	**29.8%**

Variability is reduced significantly by ~

- **Quantifying the amount of SC**
- **Reporting concentration instead of drug amount**

DPK Bioequivalence Protocol: *Japan*

Issued: July 7, 2003

Ch 2.II.1. DPK test (p. 5)

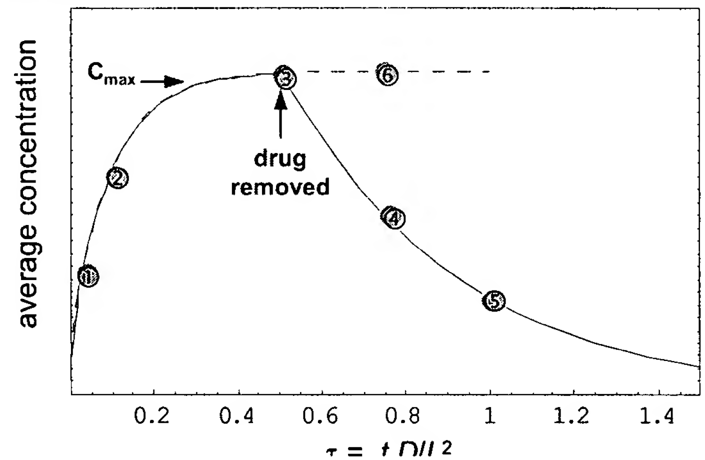
- "The amount of layers of the SC stripped off with one adehsive tape will change depending on the stripping technique of each operator and ***will vary between and within subjects***."
- "The recoveries of the SC layers … ***will be variable*** even if the ***number*** of adhesive tapes used for the stripping ***is specified*** in SOP, which lowers the power of the test. "
- "… to increase the power, it may be advantageous to use the ***average drug concentration*** …"

DPK bioequivalence: *Which metric?*

- Several different DPK metrics can be used to assess bioequivalence
  - AUC of concentration vs. time curve
  - Maximum concentration
  - Clearance rate
- Which should be used?
- Bioavailability is the rate (kinetic) and extent (thermodynamics) of absorption

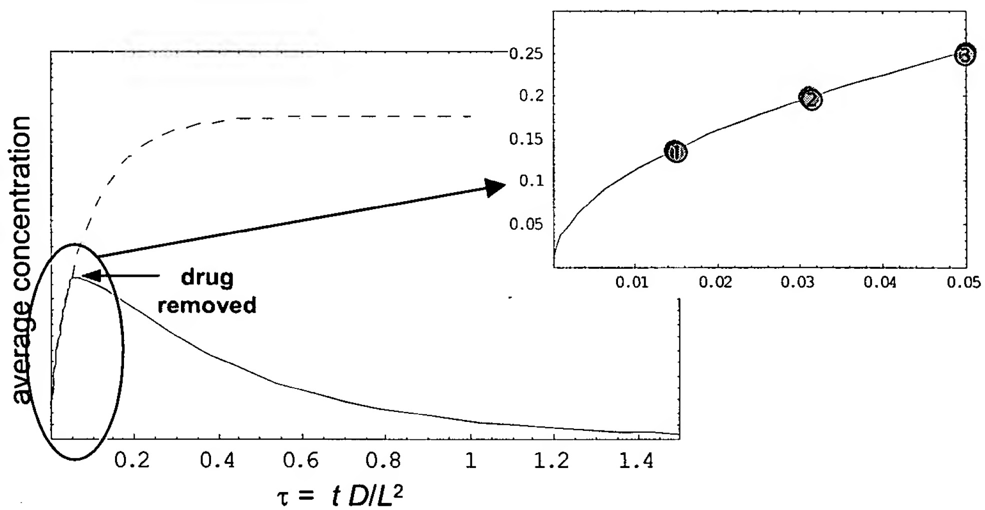
DPK bioequivalence: *Which metric?*

Uptake depends on K & D/L^2



Elimination depends on D/L^2

C_{max} depends on duration



Depending on the duration, AUC may weight uptake or elimination more

Improving the DPK method: *Goals*

- Reproducible within and between laboratories
- Minimize the number and the extensiveness of required tests
- Optimize the test design to produce maximum information at minimum cost
- Can be set up in any testing laboratory with reasonable scientific skill
- Has a sound basis in the mechanisms of drug delivery to the SC
- Provide the simplest possible information structure required for a regulatory decision

Improving the DPK method: *Issues*

- Quantification of SC collected
- Quantification of SC thickness
- Control of drug application area
- Method for reproducible drug application
- Protocol needs to be as explicit as needed and no more

Improved DPK method: *Experiments*

- Drug: Clotrimazole (Lotrimin 1% cream by Schering Plough)
  - Antifungal
  - Safe and effective for treatment of athlete's foot, jock itch & ring worm
  - SC is the site of action
- Measure
  - L (thickness of SC)
  - x (location of each tape strip within the SC)
  - ℓ (total amount of SC collected)
  - Amount of drug on each tape strip (HPLC method available)
- Goals
  - Quantify variability
  - Relate variability to mechanisms of dermal absorption
  - Develop methods for reducing variability

Improving the DPK method: *Team*

- Professor Annette Bunge, CSM
  - ¤ Professor of Chemical Engineer
  - ¤ Dermal absorption experiments
  - ¤ Mechanistic modeling of dermal absorption
- Richard Guy, U Geneva
  - ¤ Professor of Pharmacuetical Chemistry
  - ¤ Dermal absorption measurements of pharmaceutical products

Summary

- DPK is a potentially powerful technique
  - May permit facile determination of topical bioavailability/ bioequivalence
  - Allows comparison of formulations
- DPK is a new technique and needs further development
- Variability needs to be reduced
- Validation is required!

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Filed: August, 17, 1999
Exhibit C - Page 1

PATENT
Attorney Docket No.: DERM1100-1

EXHIBIT C:

PRMA (1998), "DRAFT GUIDANCE FOR INDUSTRY ON TOPICAL DERMATOLOGICAL DRUG PRODUCT NDA'S AND ANDA'S -IN VIVO BIOAVAILABILITY, BIOEQUIVALENCE, IN VITRO RELEASE AND ASSOCIATED STUDIES: DERMATOPHARMACOKINETICS (DPK) METHOD ISSUES:" http://srpub.phrma.org/letters/08.17.98.topical.derm.html

Pharmaceutical Research and Manufacturers of America
General and Specific Comments
Docket No. 98D-0388; Draft Guidance for Industry on Topical Dermatological Drug Product NDA's and ANDA's -In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies;

August 17, 1998

General Comments:

Dermatopharmacokinetics (DPK) Method Issues:

There are limited data concerning the correlation of DPK (stratum corneum stripping) data with clinical safety and efficacy. In order for the DPK method to be acceptable for a particular class of compounds or dermatological indications, a correlation between DPK and existing measures of clinical safety and efficacy must be adequately demonstrated.

There are no DPK data correlating to concentration at target tissue (epidermis/dermis 1 hair follicle).

There are inadequate DPK data correlating results in normal skin versus diseased skin.

DPK data from a homogenous population (age, sex and skin type) can not be extrapolated to the population at large. DPK on volar forearm or back (moderately permeable skin) may not be extrapolated to other body sites, with either greater or less permeability There are clear data demonstrating that DPK will fail to predict safety and efficacy for drug products that are delivered to and through hair follicles. Comparisons of DPK to BA/BE for oral drugs are inappropriate.

The reservoir for oral dosing is the gastro-intestinal (GI) tract, not blood. Most oral dosage forms are not for indications where GI mucosa are abnormal. Blood concentration is in equilibrium with target tissues for oral drugs; Stratum corneum is not in equilibrium with target tissues in skin, which is a reservoir. The DPK model does not assess the known vehicle impact on safety and efficacy. The test product must meet Q1 and Q2 for the reference product.

Safety and efficacy requirements must be addressed and met.

Single dose assessments are inappropriate for topical drugs applied in a sub-acute or chronic fashion, especially for products which impact the SC.

BA/BE must be assessed after single dose and at steady state as required for oral drugs.

BA/BE must be assessed at clinical dose levels.

The effect of occlusion, often required in the clinical treatment, on BA/BE must be addressed. DPK does not appear appropriate for combination products, especially when the active ingredients have different target sites. The single dose exposure to the drug product proposed in the draft guidance is inappropriate for complex formulations (biphasic systems, liposomes microsponges, specialized delivery excipients, etc).

DPK is inappropriate for vaginal, nail, transdermal and mucosal products.

In vitro Release Issues:

The in vitro release test (IVRT) is not measure of in vivo bioavailability should not be included in the draft guidance.

IVRT is not a surrogate for BE as noted in SUPAC-SS

The in vitro release test (IVRT) should not be used for BE of lower strength products.

Applying IVRT for lower strength qualification inaccurately assumes no changes in the physical form product.

Correlation must be established with multiple points not by a single point, as suggested in the draft Guidance.

Validation Issues for DPK:

There is a lack of data validating the proposed DPK method as a reliable, precise and accurate predictor of clinical safety and efficacy, and therefore the BA/BE for topical drugs.

The test method must be validated across investigation sites.

The template validation protocol in the draft Guidance does not address factors critical to DPK, such as time of exposure to steady state, site of application, types of tape used, number of strips, etc.

A solution, as proposed in the pilot study section, cannot be used to validate the protocol.

There is no basis for using a correction factor to deal with products found to be unstable

during a clinical study.

There are data which demonstrate large inter-strip variation in amount of SC removed.

The proposed 10 strip samples only represent a small portion (<20%) of SC. This brings into question whether the proposed protocol accurately reflects the SC drug levels. At least 85% removal of SC has been suggested as an appropriate sample.

Lateral diffusion is not accounted for by the proposed DPK method.

Statistical considerations:

There is no basis for widening Cmax of the test product to 70 to 143% of the reference product.

The guidance needs to present a better definition of how zero values should be handled in log transformation.

Specific comments on the guidance:

Specific comments on the guidance are provided below and are referenced to the particular section of the guidance they address.

I. Introduction

Given the potential for wide applicability within CDER, the guidelines should reflect a consistent approach that would be not only acceptable to the principal reviewing divisions (Dermatologic/Dental and Generic Drugs), but also be consistent with review criteria employed in other divisions. This is especially crucial for applications for drug products which may be reviewed by other divisions, but which are dermally applied. In response to the last comment in the introduction, we note that not all topically applied drugs are "locally acting," therefore those that are not should be excluded. Nicotine, nitroglycerin and estrogen patches are a few examples. Further, the systemic safety of dermatological drugs is the result of activities that are not local.

II. Background

The draft guidance comments that systemic bioequivalence is usually not feasible for topical dermatologic drug products because they generally do not produce measurable concentrations of active drug substances or metabolites in bodily fluids. However, there is a more central reason why systemic PK evaluations are inappropriate for efficacy BE determinations of topical, locally acting dosage forms. We agree that systemic measures of drug availability are irrelevant to an assessment of efficacy since the site of action of the drug is within the skin and its appendages (although systemic measures are important for safety determinations). However, it is the low level of the active drug substance or its metabolites in the body fluids that establishes the safety of many of these drug products. For orally administered drugs, the blood stream is the route by which the drug reaches its site of action, and blood levels achieved have been correlated with efficacy.

The preference for dermatopharmacokinetics (DPK) over clinical BA/BE studies, as outlined in the guidance, is not supported by the available scientific information. In order to be acceptable for a particular class of compounds or dermatologic indications, the procedure needs to be adequately validated, and shown to correlate with existing measures of clinical efficacy and safety.

At present, the appropriateness of DPK as a surrogate BA/BE method should be considered on a product-specific basis, as determined by the reference listed drug (RLD) reviewing division.

III. Inactive Ingredients
III.A. Safety Studies

When the innovator will propose formulation changes for topical drugs that require the use of new excipients, FDA's Division of Dermatologic and Dental Drug Products (DDDDP) frequently requests additional preclinical testing in addition to a clinical assessment. In these situations, inactive ingredients may be common to other NDA drugs, but new to the specific topical drug under consideration. The Agency's rationale for requesting this additional testing (both chronic and acute) is that the vehicle, i.e., the inactive ingredients, can exert a significant effect on the safety and efficacy of topical drugs.

Topical dosage forms are manufactured by a range of different formulation techniques and may consist of specialized types of finished products. It has long been known that drug bioavailability and effects vary, depending upon the vehicle in which the drug is formulated. (For example, see Pepler, et al. (1971)). The DDDDP recognizes the importance of the effect of drug vehicles on drug activity. FDA's standards for the testing of reformulated topical drugs should be consistent for the approval of innovator reformulations and for the approval of generic drugs. The safety of a potential generic product that differs qualitatively from the reference listed drug (RLD) cannot be adequately assessed by DPK. Preclinical and clinical studies need to be conducted. Again, the RLD reviewing division should determine the scope of testing required.

The draft guidance minimizes the importance of blood levels in the assessment of bioequivalence. While it is true that the systemic circulation may not be the target for topical products, truly bioequivalent products should give equivalent blood levels for the drug. Evaluation of systemic exposure on clinically relevant measures of systemic exposure is also essential to assess safety. These types of studies will require multiple doses according to the intended label rather than the single dose method described in the draft guidance.

III.B Waiver of Bioequivalence

Section III.B provides for an *in vivo* bioequivalence waiver in cases where inactive ingredients in a solution formulation do not vary more than ± 5% of each ingredient and the total formulation (see SUPAC-SS). If this is permitted, it is essential that FDA realize that this waiver should apply only to true solutions and should not be extended to other dosage forms. For example, micellar solutions are not true solutions.

The document does not clearly address the Q1 and Q2 criteria for topical products that are not true solutions (e.g., a solvent or mixtures of solvents and drug). Any generic topical product should meet the Q1 and Q2 criteria of the innovator product. For example, it appears that this draft guidance would allow DPK to demonstrate bioequivalence of a generic cream formulation to an innovator ointment formulation. That is clearly not appropriate based on the limitations of the DPK method and the effect that vehicles have on the skin.

As mentioned above, the vehicle can often have significant impact on topical drug activity. For this reason, we request that the Agency place equivalent requirements for approval on both generic drugs and innovators when determining bioequivalence testing needs. Modifications in levels of excipients (not just drug actives) can significantly alter topical drug activity. For example, the potency enhancement resulting from an increase in propylene glycol excipient concentration was of such magnitude for betamethasone dipropionate that the enhanced formulation (Diprolene) carries a different generic name (augmented betamethasone dipropionate) than the original formulation. Other excipient modifications may or may not have the same magnitude of effect, and this needs to be studied. Any changes in the qualitative or quantitative formulation should be referred to the RLD Reviewing Division (see III.A above).

IV. Bioavailability and Bioequivalence Approach

IV.A Clinical trial approaches

When bioequivalence is a question, for example in the case of a reformulation in the preapproval or postapproval phase of development, clinical studies in both normal and diseased skin may justifiably be needed. The use of surrogate measures of efficacy and safety would be both time- and cost-effective. However, since neither DPK nor *in vitro* release are validated as safety and efficacy surrogates, they should not be applied to questions of BE. (See comments at IV.D and V.)

IV.B Dermatopharmacokinetic approaches

For a new or revised test method to be considered validated, it should generally meet several important criteria. The relationship of the test method's endpoint(s) to the biologic effect of interest must be described. A detailed protocol for the test method must be available. The extent of within-test variability, and the reproducibility of the test within and among laboratories must be demonstrated. The test method's performance must have been demonstrated using reference drugs representative of the variety of agents expected to represent the full spectrum of activities for which the methods will later be applied. Further, sufficient data should be generated to permit a comparison of the performance of a

proposed substitute test with that of the test it is designed to replace.

After a review of the available data, we find that DPK studies to date: have used a variety of protocols; have not been well evaluated for within-test; within-laboratory or between-laboratory variability; and have not been evaluated for performance against a significant number of drugs to support an adequate comparison with the tests that they are designed to replace. Further, where comparisons of DPK with efficacy or pharmacodynamic measures have been performed, the DPK model has not been found to effectively predict the actual clinical trial outcomes.

The correlation between DPK and clinical efficacy and safety of topical drugs is not adequately established.

While only limited data are available regarding DPK and clinical endpoint relationships, we have evaluated this exploratory work relative to the use of DPK proposed in this guidance. Pershing, et al. have published three reports using commercially available betamethasone dipropionate ointments and creams to determine the variability and correlations between tape stripping, chromometer subjective analysis and visual skin blanching in human subjects. Conflicting results were obtained. In two of the three reports, no statistically significant correlation between stratum corneum concentration and skin blanching was observed (Pershing & Lambert, et al. (1994, 1992) versus Pershing and Silver, et al. (1992)). Moreover, in the single report supporting a correlation, a clinically irrelevant dose (159 mg/cm^2 under occlusion) was utilized. Pershing, et al. summarize in the most current report (Pershing & Lambert et al. (1994)), that quantification of drug uptake, retention in and elimination from the stratum corneum alone may be insufficient to account for clinical responses.

In a separate report, Pershing, et al. (1994), using DPK, found a constant concentration of miconazole in the stratum corneum (SC) (1.4 $\mu g/cm^2$) for the period 1 to 24 hours after drug removal. The bioactivity of miconazole on *Candida albicans* decreased 10-fold over this period of time. The 10-fold decrease in bioactivity with the constant miconazole concentration shows a lack of correlation between bioactivity and SC concentrations for the drug.

A full report of the results of DPK studies, were presented at the September, 1997 AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms - Methods of Evaluation of Bioequivalence by Louise Latriano. This work examined the effect of minor formulation and manufacturing changes on the profile of retinoid concentrations in the various tissue layers. The results of these studies showed clearly that there is no correlation between the amount of compound in the stratum corneum tissue and the amount in the epidermis, dermis, or combined dermal and epidermal tissue (r= 0.02.0.66) at the time points investigated. In addition, minor changes in manufacturing and/or the formulation were found to alter concentrations in the different skin compartments, these changes did not correlate with that found in the tape stripped stratum corneum. These studies concluded that one cannot, therefore, use the stratum corneum concentrations to predit\ct what is in the epidermis or dermis (the target site for many dermatological products).

As will be discussed in more detail in following sections, work by Parry, et al. (1992) with acyclovir found no relationship between stratum corneum concentration and antiviral efficacy subsequent to oral and topical administration.

There are clear data demonstrating that the Proposed DPK Method will fail to predict safety and efficacy for drugs primarily delivered through Hair follicles.

If DPK is to predict BE of follicularly active or follicularly delivered drugs, evidence needs to be

presented to show that stratum corneum concentration reflects follicular concentration. Follicular delivery needs to be differentiated from delivery through the stratum corneum/epidermis and delivery to the follicle by the skin vasculature. Prof. Hans Schaefer, in the March, 1998 presentation on DPK to the Dermatologic and Ophthalmic Drugs Advisory Committee, noted clear-cut differences in the permeation of several different drugs through normal rat skin (which contains hair follicles) and scarred rat skin (which does not).

Further, Schaefer, et al. (1996) have demonstrated differences in recovery of hydrocortisone, triamcinolone, and dinitrofluorobenzene from follicular casts and skin strippings. They found that the ratios of follicular concentration to stratum corneum concentration varied from 2 to 37-fold as a function of drug and time. This indicates that follicular delivery represents an important pathway for percutaneous absorption for these products especially given the high level of follicular blood perfusion. Since the stratum corneum concentrations do not reflect follicular concentrations, their usefulness for establishing BA/BE of formulations for treatment of follicular diseases (e.g., acne, hair growth, etc.) is questionable. Thus, DPK may fail to detect safety and efficacy differences resulting from differences in follicular delivery.

Hueber et al (1994) studied *in vitro* skin permeation of progesterone, testosterone, estradiol, and hydrocortisone in scarred skin versus the surrounding normal skin of human subjects. The scarred skin differed from the normal skin as it was devoid of hair follicles and sebaceous glands. The permeation (flux) of these steroids in normal skin was higher than that of scarred skin. However, the accumulation of drug in scarred skin and normal skin was not different. This paper demonstrates the importance of appendageal transport. It showed no correlation between skin accumulation and flux. Therefore, elimination of drug from the stratum corneum and presumed delivery to the skin may not reflect the actual drug in the follicle. Given the high level of vascular perfusion of follicles and sebaceous glands, this route of skin delivery is likely to be a significant route of systemic delivery for certain drugs. Based on the available data, DPK can not be expected to detect differences in follicular delivery. DPK might, therefore, show as equivalent to the RLD, a test drug that actually has higher levels of follicular delivery and result in higher systemic levels of drug. Thus, beyond the expectation that DPK will not effectively predict efficacy equivalence for follicular or sebaceous diseases, the data demonstrate that DPK will not effectively detect potential safety inequivalence.

To justify the DPK approach, several different types of studies are cited in the draft guidance. In one study, a correlation was found between the amount of compound in the stratum corneum of hairless rats 30 minutes after dosing with the amount of drug predicted to be absorbed in these animals (Rougier and Lotte, 1993). This correlation was shown under the ideal conditions of the study, i.e., for hydrophilic, permeable compounds and solutions. It has been noted that "it (DPK) has not been accepted or recommended by the regulatory agencies in bioequivalence determinations, possibly because of its apparent limitations in the area of very lipophilic drugs (e.g., retinoids or antifungals such as ketoconazole) where the quantity measured is too low" (Jamoulle and Schaefer, 1993). Even for the model compounds used in the aforementioned study, (caffeine, benzoic acid and acetylsalicylic acid) in vivo human studies indicate that under ideal conditions the correlation between amount of drug in the stratum corneum and "predicted" percutaneous absorption is low ($r = 0.7$) (Rougier and Lotte, 1993). It should also be noted that the DPK method as used above was a surrogate for systemic absorption, and not for the concentration of drug (and/or active metabolites) at the possible target sites in the skin. As stated on page three of the draft guidance, "measurment of the active moity(ies) in blood or urine is not regarded as an acceptable measurement of BA/BE for dermatological products, it may be used to measure systemic exposure." Thus, the work of Rougier cited in the draft guidance does not provide any information on whether a correlation exists between startum corneum concentrations and those in the epidermis, dermis, pilosebaceous glands, hair follicle or any other skin appendage that may be a site of action for dermatological products. The use of stratum corneum concentration to correlate to systemic

exposure as suggested by Rougier studies is questionable. The Rougier 1983 and Rougier 1990 studies were done with solution formulations containing highly penetrable excipients such as ethanol, ethylene glycol + 10% Triton X-100 in hairless rats. The relevance of these animal studies to humans is questionable.

The Rougier 1986 study was done with the highly penetrable compound - benzoic acid in ethylene glycol + 10% Triton X-100 solution formulation. Application of these results, where a single compound and a single solution formulation, to all topical drugs and topical dosage forms (cream, lotions, gels, suspensions, liposomes, etc.) is questionable

The DPK model will not detect vehicle excipient effects on clinical safety and efficacy.

Vehicle effects are considerable for topically applied products. For example, studies of tretinoin in the treatment of acne and the signs of photoaging, and minoxidil for the treatment of androgenic alopecia have shown significant vehicle effects. Aly, et al. (1989) observed a higher clinical and mycological cure rate with vehicle than active (1% ciclopirox lotion) in the treatment of plantar tinea pedis at the end of treatment.

This example clearly demonstrates that the activity of locally acting topical drugs is a composite of active and vehicle. The effectiveness of the product cannot be assessed solely by the ability to deliver drug to the stratum corneum.

The DPK method is inappropriate for drugs that are complex formulations and is expected to fail in predicting the safety and efficacy for these drugs.

The use of DPK as a surrogate for bioequivalence has not been adequately evaluated in complex formulations or delivery systems. For example, the complex release kinetics from microsponges, tapes, or even microfine suspensions may not be adequately captured in simple DPK studies.

While dissolved drug from "biphasic" formulations may permeate into the skin readily, the suspended drug must first be dissolved into the vehicle and/or skin lipids before being absorbed. Thus, permeation is not a linear function of concentration and time, and DPK would need to address the complex time course of delivery of drug to the skin.

The application of a simple, acute DPK model is even more problematic when one considers the increasing use of complex systems such as tapes, patches, microsponges, niosomes and skin delivery devices.

The proposed DPK method is not expected to provide useful information relative to predicting BA/BE for vaginal, ophthalmologic, nail, or mucosal drugs.

It is inappropriate to include skin stripping as an assay to show bioequivalence for vaginal, nail and mucosal drug products. Skin stripping is based on the premise that delivery of the drug to the stratum corneum and its subsequent release from this structure are key aspects of the delivery of the drug to the site of action. Vaginal and other mucosae have no stratum corneum. The structure and lipid composition of the nail is entirely different from the stratum corneum.

The squamous cell layer in mucosal tissue differs in thickness and biochemistry (see Goldsmith (1983)) from the skin of, for example, the volar forearm. Metabolism of a given drug in mucosal and dermal layers is likely different as a result. Drug applied to the vagina is considered to be an occluded

application. Percutaneous absorption through the mucosal surface may be affected by interaction of the topical formulation with the secretions that protect it. Note also that disease processes may alter the composition of these secretions.

The following presents evidence that the DPK approach cannot be utilized for vaginally applied drugs.

1. Skin is quite different from vaginal mucosa, both structurally and biologically most notably because of the absence of stratum corneum. As opposed to skin, where stratum corneum presents a barrier to penetration of drug and a drug reservoir, vaginal mucosa is a hormone-sensitive, vascular, highly absorptive structure. Because of these differences, it would, of course, be inappropriate to predict the delivery of a topically acting drug to vaginal mucosa, based on its delivery to stratum corneum Determining equivalence through stratum corneum stripping may not be sufficiently sensitive to discriminate two products which could possess different absorption profiles from the vaginal mucosa. This could represent a safety issue in that a product determined to be equivalent by stratum corneum stripping could be absorbed much more readily from the vagina, compared to its "equivalent" comparator, resulting in unsafe systemic levels of drug. Stripping the vaginal mucosa in the same fashion as stratum corneum is not likely to be predictive of equivalence and would be fraught with difficulty and considerable pain. Thus, for the same reasons that ophthalmic preparations are excluded from this guidance, vaginally applied drugs should also be excluded.

2. Vaginal fluid and mucosa are significantly different chemically compared to stratum corneum. The suggested method for bioequivalence testing may not be sensitive enough to detect important differences in vaginal formulations. For drugs applied to the skin, the stratum corneum is the rate limiting barrier. The partitioning of the drug from the formula into the stratum corneum, as expressed by the ratio of the drug solubility in the formula and stratum corneum is the key to optimizing a formulation. For vaginally applied drugs the partitioning of drug from the formula into vaginal fluid and then from vaginal fluid into vaginal mucosa are key to optimizing delivery (3,4). Thus the chemical properties and volume of vaginal fluid, as well as the chemical properties of vaginal mucosa are important.

3. There is no currently validated method to determine bioequivalence through proxy vaginal measures. Investigaotrs have utilized vaginal swabs, or vaginal scrapings in an attempt to determine levels of drug in vaginal tissue (5). However, the body of work needed to correlate these values to clinical cure has not been performed and there is a great deal of variability in the results.

4. Since efficacy of locally acting drugs (such as antifungal treatments for vulvo-vaginal candidiasis) is a combination of microbiological cure and improvement or elimination of signs and symptoms, the delivery of drug to the diseased tissue is only part of the equation. The concomitant application of an emollient formulation to the inflamed tissue, can have an impact on elimination of symptoms. Thus the overall cure rate will be affected by the type of formulation (e.g., emollient cream, emollient suppository or solid insert, with or without vulvar cream). Again, a dermatologic model may not be sufficiently sensitive to discriminate between two different vaginal formulations.

5. Utilizing systemic bioavailability data to predict cure of locally acting drugs suffers from the other limitations. The ideal vaginal formulation would deliver high local levels of drug with minimal systemic absorption. No data correlate systemic levels with local effect. Additionally, there has recently been a question of whether vaginal administration of drug results in high levels of drug at the uterus, compared to systemic administration.

Since ophthalmic preparations were considered unsuited for a DPK approach due to similar structural differences between stratum corneum and the anatomy of the eye, we suggest that other tissues with structural differences (vaginal and other mucosa as well as nail) are equally unsuited for the DPK approach.

The DPK method as proposed does not provide any information on the localization of drug within epidermis, dermis, and other skin structures. Different formulations may deliver drug to substantially different skin sites. Formulations with substantially different local skin site deliveries can be expected to have different efficacy and/or safety characteristics.

Parry, et al. (1992). evaluated delivery of acyclovir (ACV) to the layers of the skin following dermal and oral administration of nude mice with orthotopically grafted human skin. Topically administered drug produced strateum corneum concentrations more than 40 times that observed after oral administration. Clinically, orally administered drug is significantly more effective than topically administered drug. This poor correlation between skin concentrations and clinical effectiveness indicates that general stratum corneum concentration kinetics may not represent the kinetics of the drug at the target site (epidermal-dermal junction in this case). Again, these data show that DPK cannot predict localization of drug in the follicle.

Another example of the importance of skin site delivery is seen with local (topical) anesthetic products. Anesthesia is an individual response, and may not always correspond to a specific dose of the anesthetic agent. For EMLA, the degree of anesthesia (depth into the skin as well as duration) is a function not only of this individual variability in response, but also of the size of area treated and the duration of contact between drug and treated area. Thus, simple assessment of DPK, even over a range of time points, might not adequately assess bioequivalence. A pharmacodynamic (PD) study might be more appropriate in this case.

Information from acute DPK studies on normal adult arm or back skin will not consistently predict equivalence: to diseased skin; in geriatric or pediatric age groups; following repeated exposure conditions; under clinical dose conditions; during use on skin with permeation characteristics different from the arm or back; or under occlusion.

diseased skin

The guidance specifies conducting DPK on normal subjects, using the rationale that this is analogous to the use of normal volunteers in studies to determine the BE of oral dosage forms. It has been amply demonstrated that topical drug absorption and distribution is different in healthy versus diseased skin (Wester and Maibach, 1992). Although using healthy subjects might be appropriate for oral BE studies, where the factors that determine rate and extent of absorption may not be affected by the diseased state this is not true for percutaneous absorption. The stratum corneum is a major barrier for absorption of many topical products and whether the stratum corneum is impaired will have a major effect on the rate and extent of absorption of topical dermatological products that may not be captured using healthy skin. Also to be considered in subject selection is the age, gender and skin type of the subjects. These and other variables have been shown to eafect the amount of stratum conreum removed during the tape stripping process (Reed, Ghadially and Elias, 1995; Kompaore et al, 1993).

Further, the metabolism of diseased skin may be different from that of normal skin. In psoriasis, a reduction of aryl-hydrocarbon hydroxylase activity is seen. In individuals with acne vulgaris there is an increased metabolism of testosterone to dehydrotestosterone. Studies in patients with psoriasis, a disease characterized by increased blood flow and abnormal keratinization, have shown a greater penetration

and increased urinary excretion of corticosteroid relative to unaffected skin (Zesch, et al. (1975); Schaefer, et al. (1977); see also review, Stoughton (1982)). For example, in inflammatory diseases the inflammatory mediators increase blood flow to the skin and increase the permeability of the vascular endothelium. The rate of metabolism or elimination of drug from the site of absorption may, therefore, be affected.

Thus significant metabolic and bioavailability differences between normal and diseased skin support that any DPK model should include BE evaluations on diseased skin.

geriatric or pediatric

FDA requirements for initial approval of NDAs mandate discussion of relevant dosing, efficacy and safety information as it applies to pediatric and geriatric populations and to gender differences, if any differences have been demonstrated. Studies need to enroll sufficient patients in these subpopulations to determine whether special labeling is required.

Generic applications or supplemental reformulations of these products should determine whether the original conclusions regarding the need for special labeling are still justified. Age and gender differences have been identified in skin histology, biochemistry, and pharmacodynamic responses as well as traditional safety and efficacy parameters. These important age and gender related differences are appropriately evaluated in oral BE studies. Studies to assess BA/BE should determine whether the reference and test drugs retain the same profile regarding any differences that were identified in the original application.

Present knowledge recognizes that skin is not a simple passive barrier and that the structure of the skin changes significantly in the aging process. The interaction between the skin, the active drug, and the excipient present in the dosage form increase the complexity of evaluating the bioavailability of formulations applied to the skin.

For example, the percutaneous absorption of relatively hydrophilic compounds such as hydrocortisone, benzoic acid, aspirin and caffeine was low in the elderly (> 65 years) as compared to young adults (Roskos, et al. (1989)). In contrast, there was little age dependency observed in the percutaneous absorption of lipophilic compounds such as testosterone and estradiol.

Thus, BA/BE needs to be conducted in the subjects with the same age and gender distribution as that described in the RLD package insert.

repeated exposure

The single application test described in the BA/BE guidance appears inappropriate. Percutaneous absorption of some products does not change with repeated dosing, while for others it does. For example, the data presented in approved labeling for Tazorac (tazarotene gel) notes that single unoccluded applications of radiolabeled gel in psoriatic patients produced less than 1% systemic absorption, while repeated doses over 14 days resulted in nearly 15% absorption. Wester, et al. (1994) noted increases in excretion of applied drug following multiple versus single applications of Azone.

Therefore, any BA/BE assessment should use both acute and repeated (e.g., 14 days) exposure.

clinical dose

The guidance specifies an application "dose" of 5 mg/cm^2. It is more appropriate to vary the dose to represent low and high application amounts. Data from *in vitro* percutaneous absorption studies demonstrate a difference in absorption from "infinite" versus finite doses of drug product. More importantly, *in vivo* studies (Jackson, et al. (1989)) have shown that application amount is critically important in pharmacodynamic response.

During clinical use, topical products may be applied with variable thickness. When the applied film is quite thin, the composition of the dosage form can change dramatically as some components of the formulation evaporate into the atmosphere or are absorbed into the skin, or as skin lipids or water vapor diffuse into the vehicle. The components of the formulation may precipitate, and if the vehicle is an emulsion, it may break or undergo phase inversion. Thus, the thermodynamic activity of the drug can change throughout the period of application. Thus, any DPK model should not be confined to a fixed dose. Rather, dose proportionality should be evaluated with a range of application amounts (e.g. 0.5, 2 and 5 mg/cm^2).

body site variation

Regional variation in percutaneous absorption is well known (A. Rougier, et al. (1986), Stoughton (1989), Aly, et al. (1989), and Wester, et al. (1994, 1998)). One should not assume that any two formulations would show the same relative response when applied to different areas of the body.

Pharmacodynamic response can also vary by skin site. The dorsa of the feet and hands, elbows and knees respond poorly to corticosteroids, but respond better than the palms and soles, which rarely respond at all to topical products (Stoughton (1989)). Lesions on the upper thighs respond better than lesions on the lower legs; lesions on the chest better than those on the upper arms and those lesions on the face respond best of all. Similarly, ciclopirox lotion, 1%, is effective in interdigital tinea pedis, but is not effective in plantar tinea pedis (Aly, et al. (1989)).

These known body site variations in permeability and clinical response suggest that DPK measures on the volar forearm may not ensure bioequivalence in less (e.g. elbow, knee, and soles of feet) or more (e.g. face, scalp, or scrotal) permeable skin regions.

under occlusion

Products applied under occlusion must be studied under conditions of use, utilizing the same occlusive material used with the RLD. Tape and patch delivery systems provide an occlusive environment which affects the structure and function of the stratum corneum, and the rate of delivery of the drug to the skin. Further, vehicles may deliver drug differently when used in occluded versus open application. For example, Tazorac absorption increases from less than 1% to 5% with occlusion (package insert).

Thus, for some drugs, it may be necessary to evaluate bioequivalence both under occlusive and open application.

The statistical evaluation criteria need to be consistent with Agency standards for bioequivalence

The use of the Schuirmann two one-sided tests approach for establishing bioequivalence is an excellent one, since the alternative hypothesis rightly is the one of equivalence.

Historically, the upper and lower limits of the 90% confidence interval of the difference between the mean test and reference had to fall within ± 20% of the reference drug (or 80% and 125% if ratio of

means is used, i.e., log transformation). It is unclear why the tolerance of the ratio in the proposed guidance has been liberalized to 70 - 143% for C_{max}. This liberal interval has not traditionally been granted to any ANDA submission. FDA has routinely imposed the PK-based ± 20% (80% and 125% (log transformed) if expressed as a ratio) interval on ANDA applicants. We believe that formulations that are outside the 80%-125% range of the RLD are likely not equivalent in safety or effectiveness due to clear bioavailability differences.

IV.B.1. Performance and validation

The following detailed comments and suggestions relate to specific aspects of the DPK methodology outlined in the guidance. Many of the concerns emerging from various aspects of the DPK model have been noted previously . Therefore, they will not be restated in the following sections.

Performance and Validation of the Skin Stripping Technique

We agree that PDK studies *"should include validation of both analytical methods and the technique of skin stripping"* and support many of the recommendations made in this section regarding *"considerations for performing the skin stripping technique."* However, in addition to some of the considerations outlined, we have demonstrated that there are numerous other issues that need to be addressed in the validation of the tape stripping procedure. Louise Latriano presented the results of studies done at J&J to establish standardized procedures for the tape stripping process. The results of these studies were originally presented at the *AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms - Methods for Evaluation of Bioequivalence* (September, 1996), and at the March 19, 1998 Meeting of the DODAC.

In brief, these studies examined some of the parameters that may be important in the validation of the tape stripping assay, and determined how methodological issues in this technique may affect the pharmacokinetic analysis. These investigations revealed that even under rigorously controlled conditions, the process of applying and removing the tape strips leads to wide intersubject and intrasubject variability in the amount of stratum corneum that is recovered. This variability in the amount of tissue recovered in due to several factors: inherent variability in individual skin type and variability in SC thickness at different anatomical sites of a given individual, inherent variability in the application and removal of the tape by different "operators", and variability related to the tape selected and environmental conditions. Of these factors, those related to the variable tissue recovery are the most important. The lack of information on the percent of drug recovered from the site will have a negative impact this has on ones' ability to normalize measurements. Without a way to normalize the data for recovery, one cannot obtain meaningful numbers for the estimation of absorption or elimination rates. It is clear that such variability would only be increased in skin stripping studies conducted in multicenter fashion.

The results of this study are consistent with the results of work presented by Dr. S.P. Shrivastava entitled "Validation of DPK Methods and Standardization of Bioequivalence Protocol" at the aforementioned AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms - Methods for Evaluation of Bioequivalence (September, 1996) . In this study, conducted with multiple concentrations of tretinoin products (0.025 - 1.0%), intersubject and intersite variation in amount of tretinon recovered was high. For example, there was 7 fold (650%) difference in durg recovered in one subject from one site on the forearm to another (exact site not specified). The importance of a single person or "operator" doing the application and removal of the tape is highlighted by the finding that the profiles attained with a dose of 0.05% by one technician is similar to that obtained by another technician with the 0.025% dose. Based on this data with topical tretinoin formulations, it was concluded that the

following were "critical considerations in the standardization of a bioequivalence protocol""

- Stability of drug under test and sample storage conditions should be determined.
- Number of strips required to remove excess drug should be determined.
- Number of tapes required to remove over 85% of drug from stratum corneum should be determined.
- Drug application, excess drug removal, and drug desorption procedures should be validated.
- A standardized unit (of drug amount) should be plotted.

To our knowledge, since that Workshop no substantial new data has been generated to remove these considerations from scientific scrutiny.

IV.B.1.h

We do not believe that DPK dose response is analogous to dose proportionality studies of solid oral dosage forms. The stratum corneum serves as a reservoir of dermally applied drug, as noted by Prof. Schaefer in the March 1998 Dermatologic and Opthalmologic Drugs Advisory Committee meeting. This differs from the case of oral bioavailability studies, in which the serum is in equilibrium with the drug at the site of action. As Dr. Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products, FDA, noted in the same meeting, the analogous structure for the stratum corneum in oral bioavailability is the stomach, which is the reservoir of drug. Clearly, oral bioavailability studies place no special importance on levels of drug in the stomach.

The validation of the method calls for the establishment of a dose-response relationship using a "simple drug solution" to show the method is validated for use with the drug product. Due to the very different types of release that may be expected with a solution versus a more complicated drug formulation, Section III B of the draft guidance indicates that a topical solution drug product should be considered independently. This is supported by published results indicating that "the use of dilution methods to create a dose-response has the inherent danger of altering the physiochemical parameters of that drug in the vehicle, which may alter drug release from the vehicle, drug uptake into the stratum corneum, and the drug activity in the skin" (Pershing et al, 1994). PhRMA agrees that these two types of products have different characteristics and believes it is inappropriate to suggest that the results obtained with a drug in solution should be presumed valid for a semisolid preparation.

We disagree that dose proportionality of a solution will be relevant to other dosage forms (e.g. creams, ointments, gels). We recommend that any dose proportionality should be done in the final formulation proposed for marketing.

IV.B.1.k. Measurement of endogenous substances

The critical variables discussed in the broad scientific DPK discussion above (e.g. age, diseased skin, single versue repeated application, etc.) should be evaluated in pilot studies. This is especially important as existing data support the existence of different drug uptake and elimination profiles under these different conditions.

There is no evidence to indicate that steady state is achieved within the first 180 minutes. We propose that the pilot study phase include a determination of when steady state is achieved. Repeat dosing may be required.

IV.B.2 DPK Bioequivalence Study Protocol

IV.B.2.a Protocol and Subject Selection

It has been amply demonstrated that topical drug absorption and distribution is different in healthy versus diseased skin (Webster and Miabach, 1992). Aslthough using healthy subjects might be appropriate for oral BE studies, where the factors that determine rate and extent of absorption may not be affected by the diseased state, this is not true for precutaneous absorption. The stratum corneum is a major barrier for absorption of many topical products and whether the stratum corneum is impaired will have a major effect on the rate and edxtent of absorption of topical dermatological products that may not be captured using healthy skin. Also to be considered in subject selection is the age, gender, and skin type of the subjects. These and other variable have been shown to affect the amount of stratum corneum removed during the tape stripping process (Read, Ghadially and Elias, 1995; Kompaore et al, 1993).

IV.B.2.b Application and Removal of Test Products

We agree that an SOP must be developed and validated on the application and removal of test product as this procedure has a large influence on the repoducibility of the study. The recommendation calls for the removal of "certain oily preparations such as ointments" by "washing with a mild soap." It has been shown that for a lipophilic pesticide (alachlor) that the addition of soap reverses the partitioning of this compound into the stratum corneum (Wester and Maibach, 1992). Any procedure involved in the removal of test product needs to be validated to show that only excess drug at the stratum corneum surface is being removed and that the procedure does not affect drug concentrations in the stratum corneum.

The draft guidance suggests a fixed dose of 5 mg/cm^2. As discussed previously, we propose a dose proportionality study involving multiple doses of the RLD (reference listed drug) formulation versus the test formulation (e.g. 0.5, 2, 5, mg/cm^2) should be employed to assess the dose proportionality of the RLD formulation in the skin relative to the test formulation. In any case, the 5 mg/cm^2 dose is more than twice the accepted dose norm for topical products.

IV.B.2.d.& e. Collection of Sample and Procedure for Skin Stripping

No information supporting the validation of the skin stripping procedure and the sample collection scheme has been presented. No data has been shown that supports the premise that all excess drug is removed in the first one or two strips. The data presented in Appendix B indicates that with 10-12 tape strips only a small fraction of stratum corneum tissue is removed. This data also whow that the amount of stratum corneum removed with 10-12 tape strips can vary tremendously from person-to-person and site-to-site. The data in the attached study is consistent with published data where it was shown that after stripping with ten strips of 3M Tape, the amount of stratum corneum removed can range from approximately <5%-30% (Van Der Valk and Maibach, 1990). In; order to recoover >85% of the stratum corneum tissue (as recommended at the 1996 DPK workshop), one needs to reach the point of barrier disruption, which can require 30-67 tape strips, depending on the subject's skin type (Reed, Ghadially and Elias, 1995). In addition, the stripping properties of the skin are affected by the vehicle and it has been concluded that "the effect of vehicle treatment on stripping properties precludes one from determining drug and vehicle concentration gradients in the stratum corneum at different treatment times by direct comparison of corresponding strips." (Tsai, et al, 1991).

The important question of normalization of the amount of skin obtained has not been addressed. The Draft Guidance calls for expressing the data in amounts/area. As a standardized area is being used, the denominator or area falls out of the equation, so this approach does not address this issue. We concur with the recommendations made by Dr. Shrivastava that at least 86% of the drug should be recovered.

This would require >24 strips used in the validation study presented in Appendix B. Removing that amount of stratum corneum produces a postinflammatory response which may be followed by hyperpigmentation of the area as shown in the photograph in Appendix B. Removing that amount of stratum corneum produces a postinflammatory response which may be followed by hyperpigmentation of the area as shown in the photograph in Appendix B. We therefore question the statements that this technique is "minimally invasive".

Section IV.B.2.d (page 10) directs that all ten tape strips be combined to determine the drug content. This approach does not take into account the possibility of differential permeability within the stratum corneum between the test product and the reference product. By pooling the tape strips, the method would be unable to show potential differences between a test product that may have deeper (or less deep) penetration than the reference product. In such a situation, the test product could achieve higher concentrations deeper in the stratum corneum, closer to the epidermis or dermis, than the test product. Such a permeability-gradient difference between a test and reference product might translate into differences in drug effect and clinical efficacy and/or safety. Given these concerns, analysis should assess permeation into upper, middle and lower portions of the stratum corneum. BE should be conditioned on equivalent delivery to each of the stratum corneum regions.

The amount of stratum corneum removed per tape strip is likely to be different, which in a comparative situation could result in false positives or false negatives in terms of equivalent drug content. Thus, each tape strip should be analyzed separately to examine for possible stratum corneum gradient differences between the reference and test products. The weight of skin or the number of skin cells (possibly assessed as DNA or protein content) on each tape strip should also be determined. The drug content of the individually analyzed tape strips could be summed for total drug content for comparative purposes, but these totals should be adjusted for total skin weight differences between the reference and test product tape strips.

Section IV.B.2.d (page 10) states "These first two tape-strip(s) contain the generally unabsorbed, as opposed to penetrated or absorbed, drug and therefore <u>should be analyzed separately</u> from the rest of the tape-strips" (emphasis added). However, section IV.B.2.e (page 11) states "Repeat the application of adhesive tape two times, using uniform pressure, <u>discarding these first two tape strips</u>" (emphasis added). These two statements conflict regarding the need to analyze the first two tape strips. Formulation characteristics (e.g. substantivity, evaporation, etc.) can have an impact on clinical performance. Any significant difference between RLD and test drug in the first 2 tape strips would raise significant questions of formulation differences and change in drug reservoir such that bioequivalence may not exist. Therefore, we recommend that the first 2 strips be collected, analyzed and subjected to the statistical criterion for equivalence between test and RLD.

IV.B.3 Metrics and Statistical Analyses

As discussed above, we support the use of Schuirmann two one-sided tests approach for establishing bioequivalence. However, we believe that broadening the equivalence criteria beyond the 80%-125% (AUC or C_{max}) acceptance criteria should not be accepted.

Any selected method should be validated for accuracy and repeatability. It is unclear what information was used to derive the number of subjects needed for an initial pilot study, or what criteria would be used to establish an adequate sample size for a definitive BA/BE study using DPK. We recommend that additional research be performed to define acceptable sample sizes, especially for the pilot study.

IV.C. Pharmacodynamic Approaches

The Draft Guidance suggest a phamacodynamic approach to establish bioequivalence may be acceptable. Specifically the guidance states that *"Topically applied retinoid produces transepidermal water loss that may be used a pharmacodynamic measure to assess BA/BE."*

This approach to establishing BE for retinoids, in particular for tretinoin, was addressed at a FDA Advisory Committee on September 13, 1994. At this meeting Gary Grove, PhD., presented to the committee the results of a study conducted at the K.G. L. Skin Study Center that demonstrated that transepidermal water loss (TEWL) is an accepted measure of irritancy potential, but that irritation was not a reliable predictor of efficacy. This conclusion was based on a facial tolerance study that compared 0.1% Retin-A Cream to an experimental 0.1% aqueous gel formulation. In this study a bilateral paired comparison between left and right side of the face in 25 volunteers, selected for sensitive skin, was made after 14 days of treatment. At the end of the treatment period, the TEWL value for the subjects treated with 0.1% aqueous gel. This is in contrast to the placebo - controlled clinical studies with these two formulations (conducted separately), in which there was a similar percentage of subjects improved (reduction in overall lesion count) relative to the placebo

Transepidermal water loss measurements were also used by Penederm to compare their tretinoin formulation (Avita) to Retin-A (ref to Penederm SBA), In these studies, Penederm compared their products to Retin-A at the same strengths in the same type of formulation (i.e. cream and gel products). Although these two different Penederm formulations gave identical TEWL values when compared head-to-head to their Rdtin-A counterpart, in a clinical bioequivalence study of these Penederm products vs. Retin-A, it was demonstrated that only the Penederm cream product was bioquivalent to the innovator. These results clearly indicate the inability of TEWL measurements to distinguish between two formulations that had different clinical outcome. These findings are consistent with others that support the inability of TEWL measurements to distinguish between compounds as well as formulations. In a study entitled "Functional Changes in Human Stratum Corneum Induced by Topical Gylcolic Acid: Comparison with All-trans Retinoic Acid" (Effendy, et al, 1995), it was found that the plot of TEWL values over the eleven days of treatment with 12% glycolic acid in water was superimposable over the plot of obtained with 0.1% retinoic acid in ethanol. From this data one can conclude that these two compounds have a similar ability to alter the stratum corneum and that TEWL, as a measure of stratum corneum integrity, was unable to distinguish between them.

IV.D. *In vitro* Release (IVRT) Approaches (Lower Strength)

Sec IV.D.1 indicates that bioavailability and bioequivalence of lower strengths may be demonstrated by *in vitro* release testing. SUPAC-SS (II.3) specifically states that "*In vitro* release testing, alone, is not a surrogate test for *in vivo* bioavailability or bioequivalence.

While only limited data are available to evaluate the value of IVRT for bioequivalence determinations, evidence demonstrates that IVRT will not have a significant utility in BE determinations.

Bonina et al (1995) reported results from IVRT and *in vivo* human skin vasodilation on different methyl nicotinate formulations (solutions, gels, and liposome gels). These data show that there is no correlation between the IVRT release rate and the AUC (0 - 10 hour) for vasodilation, thus implying that IVRT is not a surrogate for BA/BE. For the methyl nicotinate formulations, IVRT could not detect significant composition changes.

Further, P. Parab (1997) showed that the *in vitro* human cadaver skin permeation could detect increases in the flux of hydrocortisone-17 valerate (HCV) with increased amounts of dimethylisosorbide in the gel formulation. The IVRT could not detect these changes, thus implying that the IVRT will not be a good

surrogate for bioequivalence; it could not detect significant quantitative changes in composition. Feldman (1997) reported the results of three studies with corticosteroid creams and ointments and found no correlation between IVRT release and the extent of vasoconstrictor responses in two out of the three cases. Lastly, DeMagistris (1997) evaluated IVRT, *in vitro* human skin flux, and skin retention of a novel development compound in different creams and gels. The correlation coefficient for IVRT release rate and skin flux was 0.14 for gels and 0.35 for creams, thus implying that IVRT is not a good surrogate for bioequivalence.

The conclusion of a joint FDA/AAPS IVRT workshop in September, 1997, included the points that:

- "...the release test is not a surrogate test for bioavailability nor bioequivalence and should only be used supportively6 (not as a primary measure) in such evaluation."
- "The in vitro release test is of no use for comparing fundamentally fundamentally different formulations (ointments vs. Creams, etc.).
- "...in vitro release is formulation (manufacture) dependent and therefore should not even be used in comparisons of seemingly like formulations made by different manufacturers. Rather the meaningful use of the release test is for showing that the fundamental properties of a formulation of given content and manufacturing method have essentially been maintained following a SUPAC-SS defined level 1 or level 2 change in the formulation."
- "There is no universal test release testing procedure (there are no universal test conditions) which is (are) applicable to all dosage forms..."

Again, since that meeting, where a clear consensus was reached, we are unaware of any new, valid, substantial, scienticaly accepted data generated to refute these issues.

Within the proposed guidance it is possible that the release rates from the test formulations are slower or faster than those of the reference formulations. The only criteria that the formulations are expected to meet is that their ratios of their release rates are similar at a given concentration. The Guidance also assumes that the physical form of the drug remains constant at varying concentrations. However, it is also possible that drug in a test formulation may exist as suspended solid and in a saturated solution at higher strength, while at the lower strength, the drug may exist only in solution. The theoretical basis for release kinetics would be different and a valid comparison could not be made between high and low strength versions.

Given the possibility that the physical form of the active ingredient may differ from one strength to another, then the current Draft Guidance is inconsistent with the SUPAC-SS Guidance as it relates to excipients. The SUPAC-SS Guidance states that if there is a change in the amount of any excipient >10% formulation to obtain a waiver for a 0.05% or 0.025% product. This would mean a change in the active ingredient of 300% would be equivalent to a Level 1 and Level 2 SUPAC change (no bioequivalence study required). As indicated in the consensus statement above, this was not an intended use for in vitro release.

In the current Draft Guidance there is also no expectation that the innovator and generic will have similar release profiles. The only criteria is to show similar ratios at different strengths. This criteria can result in the following clinical outcomes: If the generic formulation releases at a lower rate (the example cited in the Guidance) than although it may have shown bioequivalence at the highest strength, it may fail to be clinically effective at the low strength. This is because the lower release may result in drug concentrations to low to be effective. If DPK test alone were sufficient to establish BE, in the instance where the generic has a faster release rate than the innovator, and efficacy was demonstrated at the high dose, the higher drug concentrations that may be produced by the generic may produce a safety problem that was not observed with the innovator. Since classic in vivo clinical BE testing would no longer be

performed, the Agency would not be able to monitor Adverse events and may therefore fail to identify a product that has a significantly different safety profile.

"In general, IVRT does not predict bioavailability or bioequivalence." Therefore, we do not support the use of IVRT as a bioequivalence measure. The drawbacks of IVRT to predict BA/BE were presented during this workshop by T.J. Franz, T.G. Feldman, G.L. Flynn, P.V. Parab and H. Schaefer. The conclusion was that, in general, *in vitro* release does not predict bioavailability and bioequivalence.

As we have described earlier, the vehicle has clinical effects. Hence, the superiority of lower active concentration, over the vehicle, has to be demonstrated in a clinical study. This study should include the lower strength listed drug. We do not approve of IVRT being used as a surrogate for BA/BE of lower strength products once the highest strength has been studied in suitable BA/BE studies.

V. *In vitro* Release: Extension of the Methodology

Section V states that with suitable validation, *in vitro* release tests (IVRT) may be used to assess batch-to-batch product quality and substitute for other tests for drug release. SUPAC-SS (II.2) clarifies that IVRT is not required as a routine batch-to-batch quality control test.

Multiple scientific evaluations on the use of *in vitro* release have raised questions regarding its utility as a QC tool. Kundo et al (1993) found that IVRT could not detect important compositional and process changes of an isotretenoin formulation. IVRT could not detect changes in the droplet size of oil/water cream formulations from 5 - 10 microns, ± 30% changes in primary emulsifier I, + 30% changes in primary emulsifier II, or + 30% changes in water content. Thus, while the author has concluded that there is value to IVRT as a QC tool, the author's data do not support that interpretation.

Similarly, Segers et al (1997) found that IVRT could not detect changes in the composition of phenol containing ointments (with and without mineral oil) or changes in processing (such as the rate of mixing). Zatz (1995) has performed a computer based simulation which questions the sensitivity of IVRT in detecting changes in product characteristics.

Further, P. Parab (1997) found that IVRT could not detect ± 20% quantitative changes in the thickeners, emulsifier, or oil phase of ammonium lactate cream formulations and concluded that the IVRT is not a good quality control test to assure batch to batch sameness.

Therefore, the scientific data demonstrate that IVRT is not discriminating enough to be used as a QC tool.

The present SUPAC-SS guidance states that *in vitro* release testing alone <u>is not</u> a surrogate for BA/BE. Additionally, the conclusion of a joint FDA/AAPS IVRT workshop, "Assessment of value and application of *in vitro* testing of topical dermatological drug products," in September, 1997, concluded that *in vitro* release testing using a synthetic membrane is not discriminating enough to be used as a routine quality control test, and does not predict BA/BE.

The drawbacks of IVRT as a quality control tool were presented the AAPS/FDA Workshop (September, 1997)by G.L. Flynn, P.V. Parab and M. Corbo. Because of these concerns, we do not approve of the use of IVRT as a routine batch-to-batch quality control test and development and believe that validation of an IVRT are not required for approval of NDAs and ANDAs.

The IVRT permissible variance of 75 - 133.3% substantially exceeds the traditional and proposed *in vivo*

bioequivalence variance. It is generally accepted that the *in vitro* testing variance should be considerably less than a comparable *in vivo* test because of the higher inherent variability of the biological system.

This draft guidance should not supersede or expand on the uses of IVRT outlined in SUPAC-SS. Even under the current restrictions, the use of IVRT is highly controversial as clearly stated at the September 1997 joint FDA/AAPS IVRT Workshop.

VI. Systemic Exposure

Given that the drugs are approved on a "risk/benefit" basis, knowledge of systemic exposure is considered to be important. While measures of topical skin delivery might be useful for estimating efficacy between two products, this information, especially if not performed on diseased skin, under repeated exposure conditions, etc. may not provide information useful to understanding equivalency of systemic safety. Systemic availability can clearly be greater when applied to diseased skin or when repeatedly applied (see discussion above). Further, we are unaware of any substantial dataset that validates the use of acute DPK on normal volar, forearm or back for prediction of systemic exposure from repeated exposures to diseased skin or other body sites. Before DPK is adopted as a surrogate for BE, we believe that experimental data must be obtained to determine the value of DPK in assessing systemic safety equivalence.

Since safety determinations are performed with the RLD in multiple important areas (reproductive risk, animal adverse effects, clinical AE's, etc.), any significantly increased systemic exposure with a test drug (vs. RLD) would be a deviation from the RLD safety experience, require significant label changes, and bring into question the equivalence of the generic.

The critical importance of systemic safety in drug approval, mandates that systemic exposure studies and statistical demonstration of test drug equivalency to RLD be a basic requirement for all generic topical products. While FDA notes that this may be needed for some of the more systemically active topical products, PhRMA contends that any increased systemic exposure would be a significant departure from the safety experience for even less systemically active topical drugs. If this departure did exist, the risk/benefit ratio would be changed and a reassessment of therapeutic ratio and labeling would be required. In this case, a complete review of the application by the Dermatology and Dental Drug Review Division would be appropriate rather than a review by the Office of Generic Drugs.

VII. Chemistry, Manufacturing and Control

See IVRT comments in sections IV.D and V above.

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In re Application of:
Rheins and Morhenn
Application No.: 09/375,609
Filed: August, 17, 1999
Exhibit D - Page 1

PATENT
Attorney Docket No.: DERM1100-1

EXHIBIT D

AAD (1999), WASHINGTON REPORT: SKIN TAPE STRIPPING METHOD FOR GENERIC DERMATOLOGIC DRUG APPROVAL REMAINS IN QUESTION

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December 1999

Washington Report
Skin tape stripping method for generic dermatologic drug approval remains in question

Since the passage of the Food and Drug Administration (FDA) Modernization Act in 1997, the FDA has worked to accelerate the rate in which drugs reach the consumer market. The American Academy of Dermatology (AAD) has applauded this effort, because it gets critically needed drugs into the marketplace faster. How- ever, the FDA has had limited success in the speedy approval of generic dermatologic drugs.

In 1998, the FDA issued a proposed "Guidance for Industry" which urged the adoption of skin tape stripping as a means of establishing the bioequivalence of a generic topical dermatologic drug to the original brand drug. The agency considers a generic drug to be *bioequivalent* if it is absorbed into the bloodstream at the "same rate and extent" as the brand drug. The guidance document stated that skin tape stripping was comparable to traditional pharmacokinetic testing methods, which measure the amount of drug in the bloodstream and in urine.

The FDA's recommendation was very controversial and has been actively opposed by the Academy, the pharmaceutical industry, as well as by the FDA's own Dermatologic and Ophthalmic Drug Advisory Committee. The Academy believes that current data does not support skin tape stripping as a means of establishing bioequivalence.

How does skin tape stripping work?
Topical drugs are applied to the skin and a series of special strips of tape are placed over the test area and pulled off. The guidance document recommends that twelve strips be used for the test. Scientists then examine the strips to see if the drug is in the stratum corneum. Proponents of skin tape stripping contend that this method is a valid test for *all* types of topical dermatologic drugs, because the drugs are delivered so near the intended site of action. They believe that measurement of the drug uptake into and drug elimination from the stratum corneum can provide an assessment of its bioequivalence.

Proponents of skin tape stripping contend that this method is a valid test for all types of topical dermatologic drugs, because the drugs are delivered so near the intended site of action.

Opponents, including the Academy, contend that the testing methodology fails to recognize the fundamental nature of the skin—it is

not flat. Under a microscope, the skin does not have layers like a slice of French pastry; it has peaks and valley and looks more like the Grand Canyon. In testimony presented to the FDA, scientists stated that the furrows present in the skin obscure the test results and that the tape strips are mostly removing unabsorbed drug from the skin furrows. Only when scientists used more strips than was required in the guidance document (more than twenty) did they leave the skin furrows behind. More importantly, they discovered that once in the middle portion of the stratum corneum, there were statistically significant differences between the brand and generic products. If skin tape stripping is an imprecise measurement of the amount of drug in the stratum corneum, how can this method be relied upon to assess the presence of drug in the deeper layers of the skin or in the hair follicle?

Opponents of skin tape stripping have also expressed concern that the method has been used to test drugs on healthy, adult skin, while most other drugs are tested on a combination of healthy individuals and patients. The skin tape stripping technique assumes a reservoir of stratum corneum and a mechanism of penetration that may or may not be in place in diseased skin.

Opponents, including the Academy, contend that the testing methodology fails to recognize the fundamental nature of the skin—it is not flat.

Although a generic drug must have the same active ingredients, it may have different inactive ingredients. Dermatologists know that ingredients such as petrolatum may be inactive on healthy skin, but are active on scaly, psoriatic skin. Therefore, if skin tape stripping is done only on healthy skin, can we be assured that our assumptions of bioequivalence are true for psoriatic or eczematous skin?

In addition to health status, the age of the individual may also affect the ability of the skin to absorb a drug through the stratum corneum. Many dermatologists are concerned that as skin tape stripping studies are performed on the healthy skin of an adult arm, the studies may not accurately predict equivalence in the skin of the elderly or the very young. Despite the National Institutes of Health guidelines urging the inclusion of children in drug trials, the FDA guidance document remains silent on the appropriateness of this technique for children.

Despite the refusal of the FDA's own advisory committee to endorse the technique of skin tape stripping, this issue, unfortunately, remains viable.

To date, the Academy has communicated on multiple occasions with the FDA strongly questioning the validity of the skin tape stripping test. Additionally, the Academy arranged for Elizabeth Duell, M.D., a researcher at the University of Michigan, to testify before the FDA in support of the AAD's message. The Academy believes we must proceed cautiously when the health and well being of our patients is at stake and will remain diligent in opposing the use of skin tape stripping as a means of establishing bioequivalence.

2000 AAD Washington Conference slated

Academy to bring members to Capitol Hill

The American Academy of Dermatology will host a conference in Washington, D.C., June 4-5, 2000, to push issues of importance to dermatologists and their patients.

The 2000 AAD Washington Conference will include presentations on current health issues in Washington, speakers from the Senate and the House of Representatives, and visits to Capitol Hill to meet with members of Congress.

Be sure to mark your calendars for June 4-5 to attend this important event.